Pediatr Nephrol (2014) 29:1411–1416
DOI 10.1007/s00467-014-2776-9

ORIGINAL ARTICLE

Hemodiafiltration in a pediatric nocturnal dialysis program

Julia Thumfart · Christina v. Puttkamer · Steffen Wagner · Uwe Querfeld · Dominik Müller

Received: 8 December 2013 / Revised: 21 January 2014 / Accepted: 27 January 2014 / Published online: 18 February 2014

Abstract
Background To overcome the deleterious consequences of conventional dialysis, intensified dialysis programs have been developed and their feasibility and beneficial effects in children demonstrated. To investigate whether such a program can be further improved, we implemented hemodialfiltration within an established pediatric in-center, nocturnal hemodialysis program.
Methods After being started on conventional hemodialysis (HD), seven patients were switched to intermittent nocturnal hemodialysis (NHD) for 3 months, then to intermittent nocturnal online-hemodiafiltration (NHDF) for a further 3 months and finally back to NHD. Uremia-associated parameters, predialytic blood pressure, intradialytic events, protein catabolic rate and levels of albumin, vitamins and trace elements were investigated. Dialysis-related medication and dietary restrictions were also registered.
Results Phosphate and intact parathyroid hormone levels were reduced after the switch from HD to NHD and NHDF. Dialysis dose (Kt/V) was increased in patients on NHD and NHDF; however, Kt/V was significantly higher with NHDF than NHD. Blood pressure was significantly reduced in patients on NHD and NHDF despite the reduction in antihypertensive medication; albumin levels were significantly higher on NHD and NHDF, indicating improved nutritional status; protein catabolic rate was also increased. Vitamins and trace elements remained unchanged. All dietary restrictions could be lifted in patients on NHD and NHDF.
Conclusions The introduction of a nocturnal dialysis program to an existing intensified HD program significantly improved the uremia-associated parameters, nutrition and hemodynamic stability of our seven patients. At least during our observational period, hemodiafiltration was able to further improve the existing HD program by increasing the Kt/v.

Keywords Children · Hemodiafiltration · Intensified dialysis · Nocturnal dialysis

J. Thumfart · C. v. Puttkamer · U. Querfeld · D. Müller (✉)
Department of Pediatric Nephrology, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13363 Berlin, Germany
e-mail: dominik.mueller@charite.de

S. Wagner
INWT Statistics GmbH, Obentrautstraße 72, 10963 Berlin, Germany

Introduction

In children, as in adults, chronic kidney disease (CKD) and end-stage renal disease (ESRD) are associated with a tremendous increase of morbidity and mortality, as well as with a reduced longevity and quality of life. Since preemptive transplantation is not always available, children frequently face extended treatment times with either peritoneal dialysis (PD) or hemodialysis (HD). Conventional HD is performed mostly in three sessions per week, each lasting 4–5 h. However, conventional HD cannot adequately compensate renal function to prevent severe comorbidities of CKD, such as secondary hyperparathyroidism, mineral bone disorder, growth retardation, malnutrition, inflammation, hypertension, metabolic acidosis, hyperkalemia, cardiovascular disease and poor quality of life. Rather, with ongoing disease, changes like vascular calcification progress [1]. As a consequence, morbidity and mortality in this population of patients is dramatically increased compared to the general, age-adjusted population [2]. This has led to efforts to modify HD. However, neither the increase of urea elimination (Kt/V) nor the use of high flux dialysis filters over the same time period and at the same frequency has been shown to improve morbidity and mortality within a 3-year observational period [3]. A similar approach has also failed for PD [4].

Alternatively, timely extension or increased frequency, known as 'intensified dialysis,' has been demonstrated to reduce morbidity and mortality. In the pediatric setting, short daily dialysis, nocturnal home hemodialysis and nocturnal intermittent in-center programs have been established. Although having disadvantages, these modalities unequivocally show an unprecedented benefit [5–7].

Hemodialfiltration (HDF), a technique that combines convection and filtration, improves hemodynamic stability and the removal of small- and medium-sized molecular substances. Recently, studies in adults have demonstrated that high-volume HDF improved the outcome of adult dialysis patients when mortality was set as the outcome parameter [8]. Preliminary data based on clinical experience from a single center also indicate beneficial effects of HDF in the pediatric setting [9, 10]. In the study reported here, we combined intermittent nocturnal HD (NHD) with HDF (NHDF; intermittent nocturnal online-HDF) to determine the effects of adding HDF to an existing intensified hemodialysis program.

Subjects and methods

Eleven patients on the NHD program that was established in 2006 were consecutively enrolled in this prospective observational study (Table 1). Four patients dropped out because of renal transplantation in the early study period. All patients were on conventional HD (3 times, 5 h per week) for at least 3 months. These patients were included upon their wish into the NHD program (3 times, 8 h per week). After 3 months of NHD, the patients were switched to NHDF for a period of another 3 months and then back to NHD. The NHD program, including different modalities (HDF or hemofiltration) was approved in 2006 by the local ethical committee of the Charité Universitätsmedizin Berlin, Berlin. Before enrolment into the program, patients, parents and caregivers were asked for written consent. As of 2011, the NHD program became the standard HD procedure for adolescents at our hospital. Still, written consent was and is obtained in all cases. If patients or parents did not agree to the switch to NHDF, patients stay on NHD.

Table 1 Epidemiology of patients enrolled in the study

Patient	Age (years)	Gender	Underlying Disorder	Vascular Access
1	16.3	Female	HUS	Fistula
2	12.7	Male	Interstitial Nephritis	Fistula
3	15.6	Male	CyA toxicity after HTx	Fistula
4	15.2	Male	Alport's syndrome	Fistula
5	15.2	Female	Wegener's granulomatosis	Fistula
6	15.3	Male	Urethral valves	Fistula
7	13.4	Female	ARPKD	Fistula

HUS, Hemolytic uremic syndrome; CyA, cyclosporine A; ARPKD, autosomal recessive polycystic kidney disease; HTx, heart transplantation

Fresenius 4008H and 5008H machines (Fresenius SE, Bad Homburg, Germany), generating online ultrapure substitution fluid, were used for all patients throughout the observational period. The composition of the dialysate (sodium, potassium and bicarbonate) was set after initial electrolyte determination. As a anticoagulant, heparin was used in all patients; activated clotting time was regulated between 150–180 s by altering heparin dosage, if necessary. Blood flow was set at a maximal possible flow (i.e. 4–6 ml/kg body weight/min), dialysate flow was set at 500 ml/min and convective flow was set at one-third of the blood flow in the postdilution mode (Autosub+; Fresenius SE). Sodium, potassium and bicarbonate were set individually according to the patient's needs. The concentration of calcium in the dialysate was set at 1.75 mmol/l.

Serum parameters were measured four times throughout the observational period. The first measurement was taken with the patient on HD, before the switch to NHD. The second measurement was taken 3 months after the patient had been taken off HD and switched onto NHD. The third measurement was taken 3 months after the switch from NHD to NHDF. The fourth measurement was taken 1 month after the switch from NHDF back to NHD (see Fig. 1). Kt/V (via the internal online cleaning monitoring system of the machine) and predialytic urea levels were analyzed. For determining individual distribution volume (V), we used the body composition monitoring system of Fresenius.

As a marker for nutritional status we measured albumin concentration and protein catabolic rate (Table 2). For analyzing calcium phosphate homeostasis we measured calcium, phosphate and intact parathyroid hormone (iPTH) levels. Further, we measured the concentrations of trace elements (Cu^{2+}, Fe^{3+}, Mn^{2+}) as well as of vitamins (folic acid, vitamin B_{12}, 25-OH vitamin D_2, vitamin E) to investigate whether the intensified modalities (NHD and NHDF) could cause increased losses of such trace elements and vitamins.

We also assessed predialytic blood pressure (MAP), the amount of dialysis-related medication (antihypertensive drugs, phosphate and potassium binders) and changes in fluid and dietary restrictions throughout the study period. Periods of intradialytic hypotension (determined as the need for fluid bolus) were also registered. Echocardiographic changes (left ventricular hypertrophy) were investigated every 6 months.

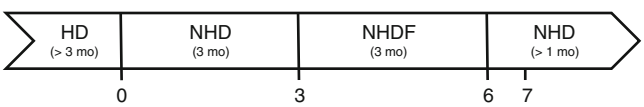

Fig. 1 Time course of the study. *HD* Hemodialysis, *NHD* intermittent nocturnal HD, *NHDF* intermittent nocturnal online-hemodialfiltration

Table 2 Medication, protein catabolic rate and intradialytic hypotensive episodes during the study (n=7 patients)

Parameters	HD	NHD	NHDF	NHD
Potassium binders	7	0	0	0
Phosphate binders	7	0	0	0
Antihypertensive drugs	7	4	2	2
Dietary restrictions	7	0	0	0
Fluid restrictions	7	0	0	0
Protein catabolic rate (g/kg/day)	0.9 (0.79–1.02)	1.2 (1.12–1.36)	1.2 (1.12–1.31)	1.3 (1.15–1.37)
Intradialytic hypotensive episodes	13	2	1	0

Data are presented as the number of episodes or as the median with the range in parenthesis

HD, Hemodialysis; NHD, intermittent nocturnal HD; NHDF, intermittent nocturnal online-hemodialfiltration

Statistical analysis

The impact of different medical treatments with respect to the measured quantity y (e.g. phosphate, Kt/V) was analyzed separately for each quantity using a random intercept model that considers individual baselines for each subject. An excellent overview of the theoretical background and the applicability of such models to the investigation at hand (including unbalanced samples) is provided by Pinheiro and Bates [11]. All statistical analyses were performed using the R statistical software (ver. 3.0.1). The models were fitted using the nlme package. The overall significance of the treatment effect was assessed using the statistics of an F test with the null hypothesis that the outcome of all treatments is identical. For quantities showing a significant F test, the differences between the treatments were tested family-wise applying the hypothesis system of a Tukey test, which was performed using the multcomp package (Fig. 2) [11–13].

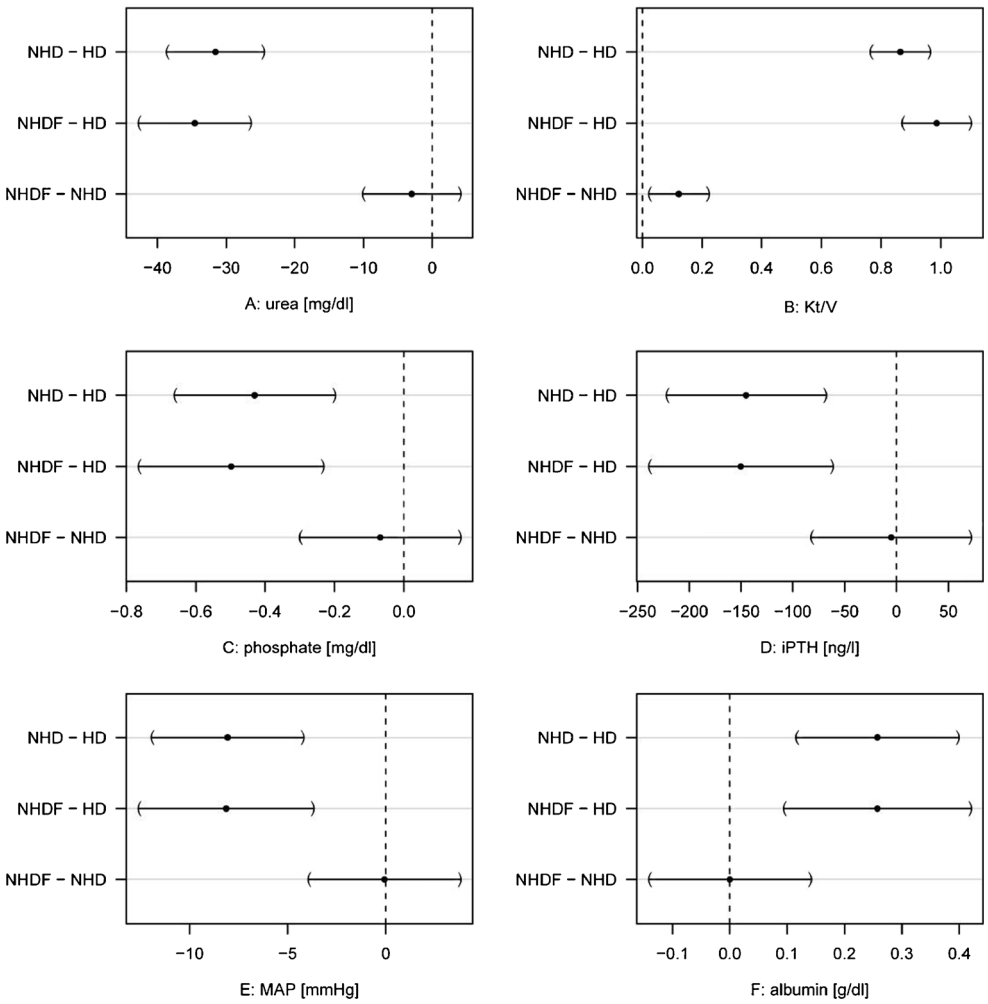

Fig. 2 Observed differences between HD, NHD and NHDF. *MAP* Predialytic mean arterial pressure, *iPTH* intact parathyroid hormone, *Kt/V* marker of dialysis adequacy, *HD*, Hemodialysis; *NHD*, intermittent nocturnal HD; *NHDF*, intermittent nocturnal online-hemodialfiltration

Results

Urea reduction and Kt/V

To determine the effectiveness of the dialysis mode, we measured predialytic urea concentration and Kt/V (Fig. 2a, b). The predialytic urea concentration of the patients under NHD was significantly lower (−31.6 mg/dl; $p<0.001$) than that under conventional HD. NHDF reduced predialytic urea concentration by 34.6 mg/dl ($p<0.001$). There was no difference in urea concentration between NHD and NHDF (p=0.6). Kt/V was significantly increased in the patients on NHD (+0.9; $p<0.001$) and NHDF (+1; $p<0.001$) when compared to conventional HD. Kt/V was significantly increased during NHDF when compared to NHD ($p<0.01$) (Fig. 2b).

Calcium and phosphate homeostasis

Serum phosphate concentration was significantly reduced in both intensive dialysis modalities—by 0.43 mg/dl with NHD ($p<0.001$) and by 0.5 mg/dl with NHDF ($p<0.001$) despite the iscontinuation of phosphate binders (Fig. 2c). Under conventional HD, all patients needed phosphate binders (Table 2). In contrast, after patients had been switched to NHD and subsequently to NHDF none of the patients required any phosphate binder. There was no difference in patients' phosphate concentration between the NHD and NHDF modalities ($p=0.8$) (Fig. 2c), and serum calcium levels were comparable in all three settings. iPTH levels were also significantly reduced in patients on NHD (−145 ng/l; $p<0.001$) and NHDF (−150 ng/l; $p<0.001$) in comparison to conventional HD. The iPTH and phosphate levels in patients on NHD and NHDF did not differ ($p=1$) (Fig. 2c, d). Vitamin 25-OH-D levels were significantly higher in patients on NHD in comparison to those on conventional HD (+26.7 μg/l; $p<0.05$), NHDF had no influence on vitamin 25-OH-D levels ($p=0.2$).

Predialytic MAP and intradialytic symptoms

We measured predialytic blood pressure as an indicator for cardiovascular risk profile. Predialytic MAP was significantly lowered (by 8 mmHg) in patients on NHD and NHDF ($p<0.001$) (Fig. 2e). When on conventional HD, all seven patients were dependent upon antihypertensive medication (Table 2). However, following the switch to NHD it was possible to withdraw antihypertensive treatment for three patients. In subsequent treatments, namely, NHDF and then later on NHD, only two patients needed antihypertensive medication. Intradialytic hypotensive phases were lower in patients on NHD and NHDF than in those on HD (Table 2). None of the patients had left ventricular hypertrophy at the end of the study (3 before entering).

Nutritional status and dietary restrictions

Serum albumin concentration was determined as an indicator for the nutritional status of the patients. We found that serum albumin concentration was significantly increased in patients on NHD (+0.3 g/dl; $p<0.001$) and on NHDF (+0.3 g/dl; $p<0.001$) when compared to conventional HD (Fig. 2f). The same was noted for protein catabolic rate (Table 2). None of the patients had any fluid or dietary restrictions during either NHD and NHDF. None of the patients on NHD and NHDF needed potassium or phosphate binders (Table 2), while all patients had potassium and phosphate binders and fluid and dietary restrictions when on HD. Concentrations of trace elements (Cu^{2+}, Fe^{3+}, Mn^{2+}) and vitamins (folic acid, vitamin E, vitamin B12) were similar under all three dialysis modalities.

Discussion

In this prospective observational study we investigated whether the implementation of online-HDF into an existing pediatric NHD program would further improve uremia- and dialysis-associated parameters. Obviously, pediatric studies have limitations because of the small number of patients, especially in subspecialties. However, with our chosen study design we were able to apply distinct statistical methods that enabled calculation of the significance of differences between the three treatment modalities.

In adults, it has been reported that HDF is able to increase intradialytic hemodynamic stability. Our results show that patients had fewer hypotensive episodes on NHD and NHDF than on HD (Table 2), but the results do not favor NHDF over NHD. Due to the convective (a term that originates from classical thermodynamics) volume, HDF eliminates medium-sized molecules more efficiently than HD.

Recent observational studies in adults support the notion that HDF could indeed decrease morbidity and mortality in patients in the long term. In 2006, the Dialysis Outcomes and Practice Patterns Study showed a 35 % reduction of mortality with high-volume HDF compared to HD. The recent ESHOL study also showed reduced all-cause mortality with high-efficiency HDF (>25 l per session) [8]. Since such endpoints, especially mortality, are not feasible within a pediatric setting, we limited the study to uremia- and quality of life-associated parameters.

A different approach to ameliorate morbidity and mortality in dialysis patients is to extend the time on dialysis. Different so-called 'intensified dialysis' modalities have been developed in the past, with the most common forms being short daily HD sessions (2–3 h, 6× per week), NHD (8 h, 3× per week) and long nocturnal HD sessions (8 h, 6× per week). All forms of intensified dialysis provide superior benefits for the

patient, and recent studies have shown that there is also an improved quality of life and patient survival [14–17]. All programs have also been successfully implemented in pediatric HD programs [5-7].

A logical step to further improve HD is there to combine the two approaches—i.e. to combine an intensified program with HDF. In the pediatric setting this has successfully been shown in a single-center short daily program [18]. In our study we show that most of the effects encountered are attributable to the switch from HD to NHD, rather than to the effects of HDF itself. However, HDF additionally contributes to the amelioration of some parameters; as such, it seems to be important to consider its use in intensified programs.

We observed significant reductions in predialytic urea levels when the patients were on NHD and NHDF. As the urea reduction rate (URR) does not seem to be a valuable marker for the comparison of HD, NHD and NHDF, we used predialytic urea levels. To our knowledge, there is no consensus on the value of URR in intensified programs. However, using Kt/V (determined using the software programming of the machine), we were able to show that NHDF significantly increased this value. Although there is an increasing debate about whether Kt/V accurately reflects the adequacy of dialysis, our data show that NHDF provides an additional benefit for urea elimination and, therefore, argues for adding HDF to such programs.

As in adults, abnormal mineral metabolism is a strong predictor of uremic vasculopathy and vascular calcifications [2, 19–21]. High levels of phosphorus and iPTH and the amount of calcium-containing phosphate binders are directly correlated with the presence of coronary calcifications. Our study showed that NHD and NHDF, when compared to HD, are able to significantly reduce phosphate while maintaining stable calcium levels (if the Ca^{2+} in the dialysate was set at 1.75 mmol/l), leading to a reduced Ca×P product. The necessity to increase Ca^{2+} has already been mentioned by Geary and colleagues [22]. In our study, both regimens (NHD and NHDF) led to a reduction of iPTH. The encountered effect on Ca^{2+} and phosphate homeostasis is even more remarkable given that none of the patients needed phosphate binders after being enrolled in the NHD program although they were on unrestricted diets. NHDF and NHD were equal in terms of phosphate removal or reduction of iPTH levels.

Patients on NHD and NHDF showed a significant reduction of predialytic MAP. During the study, the amount of antihypertensive drugs administered decreased; the prescription of antihypertensive drugs decreased further during the NHDF period, but this could be due to a delay in blood pressure lowering after start of NHD rather than implementation of HDF. From these results (reduction of phosphate, iPTH and MAP) we anticipate that both NHD and NHDF might slow the development of vascular changes.

Finally, we also investigated whether patients were depleted of trace elements and vitamins due to the prolonged dialysis time in the NHD program and additional loss by convective flow during NHDF, especially since the convective volume per session exceeded 30 l. However, we found no difference in the concentrations of trace elements or vitamins in any of the three settings (HD, NHD, NHDF). We found that the most logical explanation is that due to increased appetite and improved nutritional status (see results for albumin), any losses were fully compensated for. It is noteworthy that none of the patients after entering the NHD/NHDF program needed vitamin supplements.

In conclusion, these observations indicate that HDF is a promising treatment modality that allows further improvement of dialysis efficacy even in children treated with intensified dialysis. However, longer prospective studies in larger patient populations are needed to investigate whether treatment with HDF in combination with intensified dialysis translates into beneficial effects on CKD-associated comorbidities.

References

1. Oh J, Wunsch R, Turzer M, Bahner M, Raggi P, Querfeld U, Mehls O, Schaefer F (2002) Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. Circulation 106:100–105
2. Mitsnefes MM, Laskin BL, Dahhou M, Zhang X, Foster BJ (2013) Mortality risk among children initially treated with dialysis for end-stage kidney disease. J Am Med Assoc 309:1921–1929
3. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R, Hemodialysis Study Group (2002) Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 347:2010–2019
4. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, Mujais S, Mexican Nephrology Collaborative Study Group (2002) Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol 13:1307–1320
5. Fischbach M, Terzic J, Menouer S, Dheu C, Soskin S, Helmstetter A, Burger MC (2006) Intensified and daily hemodialysis in children might improve statural growth. Pediatr Nephrol 21:1746–1752
6. Geary DF, Piva E, Tyrrell J, Gajaria MJ, Picone G, Keating LE, Harvey EA (2005) Home nocturnal hemodialysis in children. J Pediatr 147:383–387
7. Hoppe A, von Puttkamer C, Linke U, Kahler C, Booss M, Braunauer-Kolberg R, Hofmann K, Joachimsky P, Hirte I, Schley S, Utsch B, Thumfart J, Briese S, Gellermann J, Zimmering M, Querfeld U, Muller D (2011) A hospital-based intermittent nocturnal hemodialysis program for children and adolescents. J Pediatr 158:95–99
8. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, Soler J, Torres F, Campistol JM, Martinez-Castelao A, Group ES (2013) High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol 24: 487–497

9. Fischbach M, Dheu C, Seuge L, Menouer S, Terzic J (2008) In-center daily on-line hemodiafiltration: a 4-year experience in children. Clin Nephrol 69:279–284
10. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A (2010) Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant 25:867–873
11. Pinheiro JC, Bates D (2009) Mixed-Effects Models in S and S-Plus. Statistics and Computing series, 2nd edn. Springer, New York
12. Pinheiro JC, Bates D, DebRoy S, Deepayan S, R Development Core Team (2013) NLME: linear and nonlinear mixed effects models. R package version 3. pp 1–113
13. Hothorn T, Bretz F, Westfall P (2008) Simultaneous inference in general parametric models. Biom J 50:346–363
14. Lacson E Jr, Wang W, Lester K, Ofsthun N, Lazarus JM, Hakim RM (2010) Outcomes associated with in-center nocturnal hemodialysis from a large multicenter program. Clin J Am Soc Nephrol 5:220–226
15. Lacson E Jr, Xu J, Suri RS, Nesrallah G, Lindsay R, Garg AX, Lester K, Ofsthun N, Lazarus M, Hakim RM (2012) Survival with three-times weekly in-center nocturnal versus conventional hemodialysis. J Am Soc Nephrol 23:687–695
16. Powe JR, Oluwaseun O, Woo YM, Padmanabhan N, Narasinghan E, Latta C, Tortolano J, Jardine AG, Geddes CC (2009) Ten years experience of in-center thrice weekly long overnight hemodialysis. Clin J Am Soc Nephrol 4:1097–1101
17. Weinreich T, De los Rios T, Gauly A, Passlick-Deetjen J (2006) Effects of an increase in time vs. frequency on cardiovascular parameters in chronic hemodialysis patients. Clin Nephrol 66: 433–439
18. Fischbach M, Terzic J, Laugel V, Dheu C, Menouer S, Helms P, Livolsi A (2004) Daily on-line haemodiafiltration: a pilot trial in children. Nephrol Dial Transplant 19:2360–2367
19. Shroff R, Quinlan C, Mitsnefes M (2011) Uraemic vasculopathy in children with chronic kidney disease: prevention or damage limitation? Pediatr Nephrol 26:853–865
20. Shroff R, Weaver DJ Jr, Mitsnefes MM (2011) Cardiovascular complications in children with chronic kidney disease. Nat Rev Nephrol 7:642–649
21. Mitsnefes MM, Barletta GM, Dresner IG, Chand DH, Geary D, Lin JJ, Patel H (2006) Severe cardiac hypertrophy and long-term dialysis: the Midwest Pediatric Nephrology Consortium Study. Pediatr Nephrol 21:1167–1170
22. Hothi DK, Harvey E, Piva E, Keating L, Secker D, Geary DF (2006) Calcium and phosphate balance in adolescents on home nocturnal haemodialysis. Pediatr Nephrol 21:835–841