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REVIEW

Intensified hemodialysis regimens: neglected treatment options for children and adolescents

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Abstract During recent years, the importance of intensified dialysis regimens has gathered increasing interest, especially after the Hemodialysis (HEMO) Study Group reported that a higher dose of thrice-weekly hemodialysis failed to improve clinical outcomes. Long nocturnal hemodialysis (three to six times per week) or short daily hemodialysis are the currently used forms of intensified dialysis. There is substantial evidence for cardiovascular and quality-of-life improvements as well as financial benefits with intensified hemodialysis. Preliminary experience with daily hemodialysis and hemodiafiltration in children has been reported. Given the continuing shortage of donor organs for kidney transplantation, the increasing incidence of end-stage renal disease (ESRD) and recognition of the deleterious effects of long-lasting ESRD, growth retardation, and poor social rehabilitation, more intensified dialysis regimens are a much-needed therapeutical option in both adults and children.

Keywords End stage renal disease · Intensified hemodialysis · Nocturnal dialysis · Children

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Case report

A 16-year-old girl started treatment with long intermittent nocturnal hemodialysis in 2005. She had expressed her wish to be included in a nocturnal hemodialysis program because of persistent problems with school attendance and long-term dissatisfaction with "routine" medical care.

End-stage renal disease (ESRD) due to hemolytic uremic syndrome (with renal, pancreatic, and central nervous system involvement) had occurred during the second year of life, and the patient was initially treated with continuous-cycling peritoneal dialysis (CCPD). A first kidney transplant was performed at age 7, but the organ was lost due to chronic transplant nephropathy after 5 years. Maintenance hemodialysis was performed for 2 years, and the patient then received a second kidney, which was lost at age 14 due to noncompliance. Standard intermittent hemodialysis (3 × 4 h per week) was again started but was complicated by gross lack of compliance characterized by chronic fluid overload with arterial hypertension, hyperphosphatemia with poorly controlled secondary hyperparathyroidism, malnutrition, and stunting (in part due to refusal of regular growth hormone injections). Further complications included insulin-dependent diabetes mellitus since the age of 12 years and severe reactive depression requiring prolonged hospitalization with continuous psychiatric support.

At initiation of long nocturnal hemodialysis (trice weekly with a weekly Kt/V 7.2); dry weight was 40.5 kg, height

149 cm (both below the third percentile); medications included ramipril, metoprolol, sevelamer, erythropoietin, and insulin. Soon after starting intensified dialysis, the patient experienced rapid subjective improvement, especially in her depressive feelings and overall well-being. She gained 2.5 kg of dry weight, all medications could be tapered or discontinued, and her hematocrit rose to 0.35 with a darbepoetin alpha dosage of 20 μg/week. At present, the patient does not want to receive another renal transplant until having achieved her educational goals. In a self-evaluation of her medical history, she has expressed her feeling that "regular dialysis was hell and I never want to go back to it again".

Comment

As exemplified by the patient described in the case vignette, standard in-center hemodialysis 3 × 4 h per week during daytime provides little, if any, educational, occupational, and social rehabilitation for many patients. Clearly, alternative hemodialysis modalities need to be developed to improve outcomes for patients with ESRD in general. If one considers the overall prognosis for adult patients maintained on standard hemodialysis, this patient's anger and depression may seem justified. Several forms of intensified hemodialysis have been developed to better satisfy the needs of the individual patient with ESRD; the issues involved in comparing these modalities are medical and social rehabilitation, quality of life, prevention of long-term complications, reimbursement, and overall outcome. We recently introduced long nocturnal intermittent hemodialysis (3 × 8 h weekly) for use in pediatric patients. In this review, we focus on results of recent clinical trials of the various forms of intensified hemodialysis regimens and summarize the pediatric experience as published thus far.

Introduction

As reported, a least of 60,992 patients were enrolled in maintenance dialysis programs in Germany in 2004; 10,975 of these died in that year; 95.1% were treated with hemodialysis (87.8%), hemodiafiltration (7.3%), or hemofiltration (0.3%). The percentage of older patients with end-stage renal disease (ESRD) increased by 16% between 1996 and 2004 [1]. In the same period, 871 children and adolescents were enrolled in a chronic renal replacement program (101 hemodialysis, 125 peritoneal dialysis, and 645 with functioning graft). Concerning the incidence in 2004, 156 children and adolescents needed chronic renal replacement therapy, 19 underwent preemptive renal transplantation, and 137 were enrolled in a hemodialysis or peritoneal dialysis program. In 2004, 105 patients underwent renal transplantation [1]. In an extensive cohort study of 381 Dutch children, Groothoff and colleagues reported cardiovascular morbidity and mortality as one of the major problems in dialysis and transplanted patients [2]. These data and the shortage of donor organs indicate the need for urgent improvement of dialysis regimens. Since the Hemodialysis (HEMO) Study Group demonstrated that modest increases in dialysis dose did not reduce mortality in patients receiving conventional thrice-weekly hemodialysis [3], intensive dialysis regimens including long intermittent hemodialysis (8 h three times per week), short quotidian hemodialysis (2–3 h five to seven times per week), and quotidian nocturnal hemodialysis (6 to 8 h five to seven times per week) have received increasing attention [4]. In general, all of these modalities can be performed in-center or at home; however, resource constraints have severely limited availability of these modalities in the in-center setting at most dialysis units.

Patient selection and modality choice

Intensified dialysis regimens are usually initiated when patients, caregivers or treating physicians feel that a higher dose of dialysis would be beneficial, or as "rescue therapy" for repeated congestive heart failure, refractory hemodynamic instability, hyperphosphatemia, or uremic symptoms on conventional dialysis [5]. Intensified in-center hemodialysis may not necessarily be the patient's first choice. A survey of maintenance dialysis patients who were well informed of the potential benefits of intensified regimens showed that only about 56% would agree to come to the dialysis facility daily and only if the benefits of quotidian hemodialysis were proven [6].

Motivation, adequate housing, and the ability of the patient or a care provider to be trained to perform the technique are prerequisites for home hemodialysis. Motivation and, for the case of daily dialysis, the ability to attend frequent treatments are the prerequisites for in-center dialysis. In the pediatric setting, many parents express their fear of handling hemodialysis equipment, of machinery malfunction and disconnection, and of leaving dialysis unattended (overnight); this attitude favors the in-center approach. Patients must be motivated to switch from the conventional dialysis regimen to a different form. On the program's side, the prerequisites for intensified hemodialysis are a dedicated team of doctors and nurses familiar with these modalities, sufficient training and clinic space, and remote monitoring facilities if the program has elected to monitor their home nocturnal hemodialysis patients. Reimbursement for intensified hemodialysis is an unsettled issue and currently one obstacle for widespread implementation of intensified dialysis modalities.

Despite some recent reports [7–9], there are no systematic studies comparing different forms of intensive hemodialysis. The advantages of quotidian nocturnal hemodialysis must be weighed against the requirement for long and frequent treatments, the potential for deficiency syndromes, long exposure to dialysis membranes and heparin, as well as night-time safety concerns. A prospective nonrandomized study of 11 patients on short daily, 12 patients on nocturnal, and matched controls receiving conventional hemodialysis for 5–36 months confirmed improvements in quality of life and blood-pressure control for both quotidian modalities and better phosphate control with nocturnal hemodialysis [10–13]. The main advantages of long intermittent hemodialysis are the favourable financial profile, the known improved hemodynamic benefits, and the increased middle molecule removal [4, 7]. There is only limited use of quotidian in-center hemodiafiltration or home hemofiltration for both adults and children [14, 15].

Blood access

All access types can be used for intensified hemodialysis, although the use of native arteriovenous fistula is encouraged over synthetic grafts and central venous catheters. Some centers use the buttonhole technique, where cannulation occurs repeatedly at the same site, often using noncutting needles guided by the tunnel tract into the fistula. The single-needle system may increase safety and patient comfort and improve access survival but can be utilized only for nocturnal hemodialysis in which low blood flow rates are acceptable. Some hemodialysis machines cannot perform the single needle technique or are unacceptably loud when performing single-needle dialysis. Infectious and thrombotic access complications on intensified hemodialysis occur with a similar or slightly diminished frequency compared with conventional hemodialysis, but randomized controlled studies are missing [16, 17].

Dialysis dosage

For all dialysis regimens as well as for all ages, the solute-removal measure correlating best to clinical outcomes remains unclear. Potential candidates include peak urea concentration, equivalent kidney urea clearance (EKR) based on the average urea concentration (TAC), standard Kt/V (stdKt/V; where K is dialyzer clearance, t is dialysis time and V is urea volume of distribution) based on the average predialysis urea concentration, and normalized Kt/V based on the average concentration of a theoretical solute diffusing slowly across intercompartmental barriers and therefore better representing larger molecules [18]. To explain the benefits of quotidian hemodialysis, these techniques have been extended to the comparison of larger molecule removal. The stdKt/V method, based on the average predialysis urea and therefore favoring the high-frequency regimens, has been used by most investigators [19]. Whereas conventional hemodialysis and peritoneal dialysis typically yield an stdKt/V of 2.0, the values for quotidian short hemodialysis and quotidian nocturnal hemodialysis are about 3 and 5 respectively [5, 19]. A weekly stdKt/V of 2 would be equivalent to a daily equilibrated Kt/V of 0.38 (six times a week) or single-pool Kt/V of about 0.5. In our center, children and adolescents achieve a daily Kt/V of 1.2 during 3 × 4 h per week and 2.4 during nocturnal 3 × 8 h per week, when blood flow and dialysate flow remain unchanged (3–5 ml/kg body weight (BW)/min and 500 ml/min, respectively). Convective techniques including hemofiltration and hemodiafiltration offer higher removal of higher-molecular-weight solutes; therefore, measures of urea kinetics likely underestimate dialysis adequacy [20, 21]. The use of about 15 l of replacement solution for daily hemofiltration 6 days a week in an average-sized patient provides a stdKt/V of about 2.0 per week, which is similar to conventional hemodialysis but lower than short daily hemodialysis of equal weekly duration [14]. The use of short daily hemodiafiltration has been associated with lower predialysis β_2-microglobulin levels [14]. Long intermittent hemodialysis is associated with increased middle-molecule removal, and furthermore, quotidian nocturnal hemodialysis offers a fourfold increase in β_2-microglobulin removal [22]. Advanced glycation end products and protein-bound molecules have been reported to decrease upon conversion from conventional to short daily hemodialysis. Whereas short daily hemodialysis reduces homocysteine levels, quotidian nocturnal hemodialysis appears to reduce these levels further [23].

Quality of life

Quotidian dialysis in adults has been reported to be associated with a reduction in the number and severity of dialysis-related symptoms, as well as a reduction in time to recover from dialysis [24]. Instruments measuring quality of life such as the Kidney Disease Quality of Life (KDQOL), the Sickness Impact Profile (SIP), the Beck Depression Index, the RAND-36, and the Short Form 36 (SF-36) method have all reported higher global quality of life in quotidian-dialysis patients [5, 25–27]. Utility scores assess a patient's preference for their current health states and are graded on a scale between 0 (a quality of life equivalent to death) and 1 (the best quality of life imaginable) [28]. Patients receiving conventional hemodialysis typically report utility scores of about 0.5, which are lower than scores reported by patients who suffer from blindness or paraplegia. Mean utility scores for patients receiving home quotidian hemodialysis were about 0.7, similar to historically reported values following kidney transplantation [10, 28]. Data from our own center demonstrated clearly an improvement in various scores of self-assessment of physical strength and social abilities. Interestingly, the same improvement was registered when parents, nurses, teachers, psychologists, and treating physicians were asked for their assessment (unpublished results). Reduced recovery time from intensified dialysis regimens is certainly an issue contributing to the improved quality of life of such regimens [24].

Calcium and phosphorus metabolism, and bone disease

Disorders of mineral metabolism contribute in many ways to cardiovascular disease in predialysis and dialysis patients. Phosphate is removed by hemodialysis less efficiently than urea due to its slow mobilization. Consequently, an early decrease in serum phosphate during hemodialysis is followed by rebound prior to and after the end of dialysis [29]. High dialysis frequency increases phosphate removal by allowing daily equilibration of the serum levels and restoring the blood to dialysate gradient. However, the main determinant of phosphate removal is the duration of dialysis. Unless dialysis time is longer than 2 h, short daily hemodialysis results in a minimal decrease in serum phosphate (and requirements for phosphate binders) and no effect on parathyroid hormone. Measurement of phosphate in dialysate suggests that phosphate removal increases with short daily hemodialysis, but patients typically increase their protein intake, which minimizes the net effect on serum phosphate levels [30, 31]. Quotidian nocturnal hemodialysis removes phosphate at an amount similar per dialysis session and therefore double per week when compared with conventional hemodialysis, allowing discontinuation of phosphate binders despite increased dietary phosphate intake in most patients [32]. Despite a liberal diet, phosphate must even be added to the dialysate to avoid hypophosphatemia in about half of quotidian nocturnal hemodialysis patients. Normalization of serum phosphate results in normalization of the calcium–phosphorus product and allows the safe increase in dialysate calcium, which can result in higher serum calcium and lower parathyroid hormone levels without the use of vitamin D analogues. Serum vitamin D levels increased in patients converted to quotidian nocturnal hemodialysis [33]. Tumoral calcinosis can resolve after conversion to quotidian nocturnal hemodialysis [34]. Higher dialysate calcium losses and the discontinuation of calcium-containing phosphate binders can result in a negative calcium balance in patients performing quotidian nocturnal hemodialysis, necessitating higher dialysate calcium concentrations [22, 35]. Dialysate calcium is increased until postdialysis calcium levels are higher than predialysis. Dialysate calcium and phosphorus can be adjusted by the patients through the addition of powdered calcium chloride or sodium phosphate, the latter being added into either the acid or bicarbonate concentrate.

In our center, children and adolescents on long intermittent nocturnal hemodialysis were able to discontinue phosphate binders. A higher phosphate intake was assumed because dietary restrictions were lifted. Adjustment of calcium and phosphate solution via the dialysate were not necessary under these conditions.

Cardiovascular disease

Improvement in blood-pressure control without or with minimal use of medications has consistently been reported in both forms of quotidian hemodialysis [5]. Current understanding of the mechanism by which blood pressure is lowered by frequent dialysis suggests that quotidian short hemodialysis lowers blood pressure primarily via enhanced extracellular fluid volume control [11, 36]. In contrast, quotidian nocturnal hemodialysis lowers blood pressure by a selective decrease in total peripheral resistance [37]. Both forms of intensive hemodialysis have been found associated with regression of left-ventricular hypertrophy not convincingly seen on intermittent long hemodialysis in adults [36, 38]. Other cardiovascular effects unique to nocturnal hemodialysis include restoration of impaired left-ventricular systolic ejection fraction [39], correction of sleep apnea and restoration of cardiac autonomic balance during sleep, improvement in flow-mediated dilation and endothelium-independent vasodilation, restoration of impaired peripheral vascular flow, and an increase in serum high-density lipoprotein levels [39, 40]. Quotidian nocturnal hemodialysis patients can suffer from persistent hypotension following renal transplantation; however, blood pressure tends to rise 12 months posttransplant in this group, whereas it tends to fall in conventionally dialyzed patients [41]. The difference in phosphate control between the two quotidian regimens may explain the dissimilar cardiovascular effects of the two regimens. The vascular responsiveness in patients before and after conversion to nocturnal hemodialysis was compared in patients with either high or normal baseline plasma phosphate levels. There was delay in the restoration of vascular responsiveness in the hyperphosphatemic cohort, suggesting that phosphate control is related to cardiovascular homeostasis. Coronary calcification, as quantified by spiral computed tomography, was unchanged 1 year after conversion to nocturnal hemodialysis, suggesting a beneficial effect of the improved uremic control and normalization of serum phosphate [42]. It has been described in an unselected adult dialysis cohort that online hemodiafiltration reduced the risk of mortality by 35% [43]. Furthermore, patients on conventional hemodialysis have a three- to fourfold decrease in endothelial progenitor cell number and function compared with matched controls [44]. In contrast, patients on nocturnal hemodialysis have normal endothelial progenitor cell number and function, suggesting that improved uremic control may restore the balance between vascular injury and repair [45]. As a clinical result of the cardiovascular benefits described above, patients on daily nocturnal hemodialysis show improvement in exercise duration and capacity [46]. In our center, none of the patients displayed left ventricular hypertrophy after 6 months of intensified dialysis, although this was present in two patients at entry into the program.

Erythropoietin dose and anemia control

Reports on the impact of quotidian hemodialysis on anemia management have been variable. Most groups described an increase in hemoglobin concentrations and a decrease in erythropoietin requirements of as much as 45% [5]. However, negative results have also been reported [25, 47]. Some were ascribed to insufficient iron supplementation or insufficient length of follow-up. In contrast to the lack of improvement in erythropoiesis in the early reports on nocturnal hemodialysis, a significant increase in hemoglobin levels and a decrease in erythropoietin requirements were recently reported [48]. In that study, 24% of patients did not require treatment with an erythropoietic agent.

Nutrition

Most patients who convert to quotidian hemodialysis experience improved appetite. Reports on the short and long-term effects of quotidian hemodialysis on serum albumin and weight are variable, with improvements seen in most, but not all, studies [6, 49, 50]. High baseline comorbidity appears to blunt the nutritional benefits of quotidian hemodialysis, and this may explain the differences in serum albumin between patients on short and nocturnal quotidian hemodialysis [23]. A relative hemodilution may be responsible for lower albumin levels at the end of the nocturnal hemodialysis sessions [51].

Sleep

Sleep disorders such as sleep apnea, periodic limb movements, and daytime sleepiness are highly prevalent in ESRD and might be considered as a marker for quality of dialysis [52]. Quotidian nocturnal hemodialysis has been demonstrated to normalize the sleep pattern in patients with prior sleep apnea [53]. However, the prevalence of daytime sleepiness did not change after conversion to quotidian nocturnal hemodialysis, nor did the frequency of periodic limb movements [54]. There are no data on the effect of short daily hemodialysis on sleep disorders.

Pediatric aspects

Early renal transplantation is the therapy of choice for children and adolescents with ESRD, limiting the time on maintenance dialysis in most cases; however, pediatric hemodialysis units frequently encounter patients requiring long-term hemodialysis. Shortage and size restriction of donor organs, previous transplant rejections (often due to noncompliance), immunological sensitization, recurrence of

Table 1 Summary of the different modalities of current intensified hemodialysis regimens and their major benefits and disadvantages

Method	Sessions per week	Duration per session (h)	Major advantages	Major disadvantages
Conventional	3	4–5	Standardized and most widespread procedure	Poor phosphate removal and volume control, poor social rehabilitation
Short daily	5–6	2–3	Superior phosphate removal and volume control	Poor social rehabilitation
Intermittent long nocturnal	3	8	Good phosphate removal and volume control, superior social rehabilitation	Intermittent procedure with restrictions of fluid intake for patient
Quotidian nocturnal	5–6	8	Excellent removal of phosphate, excellent volume control, social rehabilitation	Frequent dialysis, high costs for dialysis

the primary disease in the graft, and subsequent failure and peritoneal dialysis failure are among the most frequent reasons contributing to an increase of this difficult-to-treat population. For these patients facing years of in-center intermittent hemodialysis, both medical and social rehabilitation and quality of life are severely restricted during a most vulnerable period of life. Failure to thrive and malnutrition, impaired longitudinal growth, neurodevelopmental delay, disturbed pubertal development, and impaired social and professional rehabilitation (education, employment) are frequently observed. Moreover, morbidity and mortality from cardiovascular causes is comparatively highest in the young. Thus, given the life expectancy of children compared with adults, children and adolescents are a population in need of dialysis regimens that provide better medical and social rehabilitation; intensified dialysis needs to be evaluated in young patients with high priority. The feasibility of pediatric intensified hemodialysis programs has recently been demonstrated in Canada. In this program, it has also been demonstrated that even home hemodialysis is a suitable method in children and adolescents. Blood access was realized via a central catheter [55]. A daily in-center program for short daily dialysis has been established in Strasbourg, France [15]. Preliminary data of these programs indicate that unique benefits in children might also include better nutritional status and growth, the latter being one of the crucial problems in pediatric nephrology [56].

Alternatively, long nocturnal hemodialysis provides an attractive method, as children and adolescents can go to school or start other activities during the day. The only existing in-center program for long nocturnal hemodialysis in children was established in Berlin in 2005. In our experience, any form of intensified hemodialysis requires the child's expressed wish and motivation and strong parental support. However, historic experience shows that many parents or caretakers often cannot continuously provide home hemodialysis on a high professional level comparable with specialized pediatric dialysis centers. Therefore, in-center nocturnal hemodialysis is a logical option, especially for a city-based population. In our experience, marked improvements in medical parameters and subjective well being combined with better school attendance and overall social rehabilitation can be achieved with long nocturnal hemodialysis. Since 2005, we have enrolled more than ten patients in this program. Central catheters and fistulas were used for blood access. All patients needed erythropoetin administration before entering the program. Complications associated with the blood access (e.g. disconnections) were not encountered; all children described their sleep quality (after an initial period) as not being different from their sleep at home. All but one patient refused to switch back to daytime hemodialysis program and instead sought an adult facility offering nightly hemodialysis.

It is desirable that pediatric patients on intensified regimens are entered in an international registry, as has been successfully done for adults [57]. In this registry, established in 2004, more than 229 adult patients have been enrolled so far. Patients from three different programs are enrolled: home nocturnal, home short daily, and in-center short daily. Data of this registry will be of extreme value to determine the advantages and disadvantages of each regimen in order to identify the adequate modality for the individual patient. A comparison of intensified hemodialysis regimens is presented in Table 1.

Conclusion

Virtually all studies consistently demonstrate that intensified hemodialysis modalities provide improvement in quality of life, biochemical and cardiovascular parameters, and likely anemia and nutrition. Provided that a solution to the reimbursement problem is found, intensified dialysis is expected to become a prevalent choice in the treatment of ESRD. The role of hemofiltration may also grow. These methods will provide revitalization of home hemodialysis, bringing social and vocational rehabilitation to more patients while providing a solution to the nursing shortage prevalent in many countries. Further studies of all aspects of intensified hemodialysis are necessary to increase our understanding of the methods and provide the data necessary for their appropriate reimbursement. Given the increasing shortage of donor organs, intensified regimes reducing the side effects of ESRD are mandatory. It should be realized that standard hemodialysis provides only minimal requirements of survival with renal replacement therapy. The still limited data from pediatric centers as well as our own experience imply that intensified is an effective and safe method with superior clinical outcomes compared with conventional hemodialysis or peritoneal dialysis.

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