REVIEW ARTICLE

Intensified Hemodialysis in Adults, and in Children and Adolescents

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SUMMARY

Background: There are now almost 70 000 dialysis patients in Germany. Conventional hemodialysis does not adequately compensate for malnutrition, arterial hypertension, renal osteopathy, and diminished performance ability. Various strategies for intensified hemodialysis have been implemented in an attempt to lower the considerable morbidity and mortality of end-stage renal failure.

Methods: We selectively review the literature on intensified dialysis in adults, children, and adolescents.

Results: In a randomized, controlled trial (RCT), a group of patients undergoing conventional dialysis was compared to a group undergoing brief, daily dialysis. Daily dialysis significantly improved the combined endpoint of left-ventricular hypertrophy or death (hazard ratio [HR] 0.61). In contrast, another, retrospective study found daily dialysis to be associated with higher mortality (15.6 vs. 10.9 deaths, HR 1.6). A prospective case-control study found nocturnal intermittent hemodialysis to be associated with lower mortality than conventional dialysis (1.77 vs. 6.23 per 100 patient-years); this result was confirmed in a further, retrospective study. An RCT on nocturnal dialysis performed every night revealed a significant regression of left-ventricular mass, yet the patients' quality of life improved only in individual domains specifically related to renal function. Small-scale studies of intensified hemodialysis in children and adolescents have found that it leads to a higher growth rate and weight gain.

Conclusion: Intensified hemodialysis techniques improve arterial blood pressure, uremia-associated variables, and psychosocial variables. They also lower the necessary doses of antihypertensive drugs and phosphate binders. Dietary restrictions need not be as stringent. Further prospective trials are needed for a reliable assessment of the effect of intensified hemodialysis on mortality and quality of life.

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There are nearly 70 000 dialysis patients in Germany (1). These patients need comprehensive interdisciplinary care. Their morbidity and mortality are elevated in comparison with the normal population, especially in younger and intermediate age groups (2). The life expectancy of patients with end-stage renal failure depends on the method used to compensate for the lack of renal function. Patients who have undergone renal transplantation (mortality 3.8 per 100 patient-years) live longer, on average, than dialysis patients on a transplant waiting list (mortality 6.3 per 100 patient-years) (3). Transplantation, however, is not an option for all patients. There are markedly fewer organ donors than potential recipients, and fewer than one-third of all dialysis patients are reported to EUROTRANSPLANT for placement on a waiting list (4). Improved dialysis methods therefore seems all the more important.

In Germany, conventional hemodialysis is performed in a dialysis center—or, in rare cases, at home—for 4 to 5 hours, 3 or 4 days a week. This form of treatment often cannot adequately compensate for the sequelae of chronic renal failure, such as disordered calcium/phosphate metabolism, renal osteopathy, malnutrition, arterial hypertension, and uremic vasculopathy, even if the patient is simultaneously treated with dietary restrictions (potassium, phosphate), fluid restriction, and drugs (5–7).

The effects of chronic renal failure on the cardiovascular system, most prominently uremic cardiomyopathy and vasculopathy, are the main causes of high morbidity and mortality in dialysis patients (8, 9). These patients' social life is often severely restricted. For many, normal participation at work or in school is all but impossible.

Eknoyan et al. showed that modifying the technique of hemodialysis by, e.g., increasing blood flow or using high-flux filters does not lower mortality in hemodialysis patients (10).

Other dialysis techniques, such as continuous, ambulatory peritoneal dialysis (CAPD), seem to lower mortality at the onset of dialysis treatment (11). It remains unclear from the available evidence whether hemodiafiltration also lowers mortality (12–14).

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TABLE 1

Overview of prospective controlled trials of intensified hemodialysis

	Reference	Number of pts.	Type of study, type of analysis	BP control	Left ventricular hypertrophy	Phosphate (mg/dL)	Quality of life	Mortality
Short daily hemodialysis	FNH Trial Group et al. (16)	125	RCT, per protocol	improved	Δ -10.1 g in left ventricular mass	Δ -0.56	+ 2 points on RAND-36	lower*
Intermittent nocturnal hemodialysis	Ok et al. (18)	247	case-control study, per protocol	improved	left ventricular mass index: 116 g/m ² for NIHD vs. 139 g/m ² for ConvHD	3.87 vs. 4.96	constant (worse under ConvHD) on SF-36	1.77 vs. 6.23 per 100 py
Nocturnal hemodialysis every night	Rocco et al. (17)	45	RCT, per protocol	improved	no effect	Δ -1.4	no effect	no effect
	Culleton et al. (31)	52	RCT, per protocol	improved	Δ -15.3 g in left ventricular mass	Δ -1.5	no effect on overall quality of life; improvement in specific areas of SF-36 related to renal function	ns

When two figures are given, the first refers to the intensified technique in question, the second to conventional hemodialysis. The difference Δ is the value for the intensified technique minus the value for conventional dialysis. When only qualitative results are quoted, this is because very different variables were measured, making direct comparison impossible, or because no concrete figures were given at all. The number of patients listed is the number treated with intensified hemodialysis in the study in question.

BP, blood pressure; RCT, randomized controlled trial; RAND-36, an instrument for measuring health-related quality of life that was developed by the RAND Corporation; * combined endpoint incorporating both left ventricular mass and quality of life; ConvHD, conventional hemodialysis; SF-36, short form of the test for health-related quality of life; py, patient-years; ns, not studied

Introduction

In this article, we present the current evidence (based on a selective literature review) regarding the effects of intensified hemodialysis on the following variables:

- arterial blood pressure
- left ventricular hypertrophy
- dietary restrictions
- pharmacotherapy
- quality of life
- overall mortality.

To this end, we searched the PubMed database, using the search terms “intensified dialysis,” “frequent hemodialysis,” “short daily hemodialysis (SDHD),” “nocturnal intermittent hemodialysis (NIHD),” and “nocturnal home hemodialysis (NHHD).” In our analysis, we considered all prospective randomized trials (*Table 1*) and observational studies (*Table 2*) on adults that were published after 1998 and involved at least 30 patients, and all relevant publications on children and adolescents.

Intensified hemodialysis techniques

The first publications on intensified hemodialysis appeared 30 years ago. In Tassin, France, patients were treated with dialysis at low blood flow rates for 24 to 30 hours per week (15). All of them were normotensive, none received antihypertensive medication, and none had a myocardial infarction during the period of the study. The 10-year survival rate was 85%.

Currently, intensified hemodialysis is generally performed by one of the following three techniques:

- short daily hemodialysis (2–3 hours, 5–7 days a week)

- nocturnal intermittent hemodialysis (6–8 hours, 3 days a week)
- nocturnal hemodialysis every night (6–8 hours, 5–7 days a week).

All of these techniques can be performed either at home or in a dialysis center (*Table 3*).

All three techniques improve urea elimination and increase the clearance of intermediate-sized molecules (16–18). They enable lowering of the ultrafiltration rate; higher ultrafiltration rates in conventional hemodialysis are associated with higher mortality (19). Movilli et al. showed that patients who died within 5 years of starting dialysis had higher ultrafiltration rates than those who were still alive at 5 years (14.1 vs. 11.4 mL/kg/h) (19).

The International Quotidian Dialysis Register contains data on patients treated with different types of intensified hemodialysis (20). This initiative was also the origin of the Frequent Hemodialysis Network Trial Group, which has published 2 of the 4 prospective controlled trials on intensified hemodialysis that have been carried out to date (16, 17). The other studies provide evidence of a low level (*Table 2*).

Short daily hemodialysis

This type of dialysis is characterized by a high frequency of treatment (5–7 days a week for 2–3 hours), usually with no more than a slight increase in the number of hours spent undergoing dialysis per week. It is carried out either at home or in a dialysis center.

Kjellstrand et al. reported retrospectively on 415 patients who were treated with short daily hemodialysis for 29 ($\pm$ 31) months, either at home or in a dialysis

TABLE 2

Overview of observational studies and case series of intensified hemodialysis

	Reference	No. of pts.	Type of study	BP control	Left ventricular hypertrophy	Phosphate (mg/dL)	Quality of life	Mortality
Short daily hemodialysis	Kjellstrand et al. (21)	415	retrospective observation	ns	ns	ns	ns	Median survival time prolonged by 2.3–10.9 years
	Woods et al. (22)	72	retrospective observation	improved	ns	ns	ns	ns
	Suri et al. (24)	318	retrospective case-control study	ns	ns	ns	ns	15.6 vs. 10.9 deaths per 100 py
	Fischbach et al. (25, 26)*	5	prospective observation	improved	improved	1.28 vs. 1.87	ns	ns
Nocturnal intermittent hemodialysis	Lacson et al. (28)	746	retrospective case-control study	improved	ns	5 vs. 5.73	ns	2-year mortality 19% vs. 27%
	Bugeja et al. (29)	39	retrospective observation	improved	ns	4.4 vs. 5.3	improved (own questionnaire)	ns
	Hoppe et al. (30)*	16	prospective observation of intervention	improved	improved	1.37 vs. 2.14	improved in 4 areas of the SF-36	ns
Nocturnal hemodialysis every night	Bergman et al. (32)	32	retrospective case-control study	ns	ns	1.3 vs. 1.7	ns	ns
	Geary et al. (33)*	4	case series	no effect	ns	improved	improved	ns

When two figures are given, the first refers to the intensified technique in question, the second to conventional hemodialysis. The difference Δ is the value for the intensified technique minus the value for conventional dialysis. When only qualitative results are quoted, this is because very different variables were measured, making direct comparison impossible, or because no concrete figures were given at all. The number of patients listed is the number treated with intensified hemodialysis in the study in question. BP, blood pressure; ns, not studied; py, patient-years.

* pediatric studies; SF-36, short form of test for health-related quality of life

center, and compared their survival rates with those of patients undergoing conventional dialysis (21). Short daily hemodialysis was found to prolong the predicted median survival time by 2.3 to 10.9 years. Woods et al. reported that patients who were switched to short daily hemodialysis experienced a lowering of arterial blood pressure by 7 mmHg (systolic) and 4 mmHg (diastolic), despite concomitant reduction of antihypertensive medication (22).

No distinction was drawn between home and center-based dialysis in these two studies (21, 22). This may have led to misinterpretation of the data, as home dialysis is associated with longer survival regardless of the dialysis technique (conventional vs. intensified), probably because of selection of suitable patients (23). Patients with fewer comorbidities, higher motivation, and a more stable social environment are more likely to opt for home dialysis.

In two further studies, both short daily dialysis and conventional dialysis were performed exclusively in a dialysis center (16, 24). One of these was the single prospective, randomized trial of short daily vs. conventional dialysis that has been performed to date: it

included 125 patients in the former group, who underwent dialysis six times a week, and 120 in the latter group (16). Patients under age 18 were also included in this study. Short daily dialysis was found to be associated with improvement in both of the combined endpoints studied, i.e., regression of left ventricular hypertrophy or reduction of death rate (median difference of left ventricular mass, 10.1 g; hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.46–0.82) and improved health-related quality of life or reduction of death rate (median difference in health-related quality of life, 2 points; HR, 0.70; 95% CI, 0.53–0.92). These combined endpoints were chosen because of the brief duration of the study (12 months) and the small number of patients. Short daily dialysis did not lower mortality; rather, the endpoints were reached by regression of left ventricular hypertrophy and by an improved health-related quality of life, respectively.

The patients treated with short daily dialysis experienced an improvement in blood pressure control and normalization of hyperphosphatemia. They did, however, need intervention for vascular access more frequently than patients treated with conventional

TABLE 3

Qualitative comparison of conventional and intensified dialysis techniques

Method	No. per week	Duration (hours)	Blood pressure control	Phosphate control	Social rehabilitation	Remarks
Conventional hemodialysis	3	Europe: 4–5 USA: 3–4	limited	poor	limited	standardized, most common form of treatment
Short daily hemodialysis	5–6	2–3	good	excellent	good	undisturbed sleep
Nocturnal intermittent hemodialysis	3	8	good	good	very good	normal employment possible
Nocturnal hemodialysis every night	5–6	8	excellent	excellent	good	most demanding technique of all

dialysis (16). Only 78% of the patients undergoing intensified dialysis had more than 5 sessions a week.

In the second study that exclusively involved patients undergoing center-based dialysis, by Suri et al. (24), propensity score–based matching was used for a retrospective comparison of the mortality of conventional hemodialysis and short daily hemodialysis (in 575 and 318 patients, respectively). This is probably the most methodologically sound large-scale study of comparative mortality that has been performed to date. Patients who underwent short daily dialysis had a higher mortality (15.6 vs. 10.9 deaths; HR, 1.6; 95% CI 1.1–2.3). Possible causes include a more pronounced inflammatory reaction induced by longer exposure to dialysate and the increased physical and emotional stress associated with daily dialysis (24).

The first report on short daily dialysis in children and adolescents was that of Fischbach et al. in 2004 (25). Hemodiafiltration was carried out 6 days a week in a pediatric center (specifically pediatric data) (Table 4). The patients undergoing short daily dialysis no longer needed to restrict their diet, grew more rapidly, and required less antihypertensive medication (26). Their quality of life was not studied. The clear disadvantage of this technique is that the patients, in general, can no longer attend school regularly (27).

Nocturnal intermittent hemodialysis

Nocturnal intermittent hemodialysis (NIHD) is performed 3 nights a week for 6–8 hours, either in a dialysis center or at home. This method increases the overall time spent in dialysis without increasing the frequency of sessions. Performing dialysis at night makes its long duration less bothersome for the patient.

There has been only one prospective case-control study comparing center-based NIHD to conventional dialysis (247 patients each) (18). NIHD was associated with significantly lower mortality (1.77 vs. 6.23 per 100 patient-years, HR 0.28, 95% CI 0.09–0.85) after a mean follow-up of 11.3 ($\pm$ 4.7) months.

Blood-pressure values were the same in both groups, but the patients undergoing NIHD took less antihypertensive medication than those undergoing conventional dialysis (8% vs. 22% required antihypertensive drugs). Left-ventricular mass was significantly lower in the NIHD group (116 [$\pm$ 34] vs. 139 [$\pm$ 45] g/m²). Likewise, fewer NIHD patients required phosphate binders (22% vs. 83%). Over the period of observation, the patients undergoing conventional dialysis experienced a significant deterioration of their quality of life with respect to physical pain, mental health, and vitality, while the quality of life of the NIHD patients was unchanged. 19% of the patients initially treated with NIHD abandoned this form of treatment because they found center-based NIHD to be too cumbersome (18).

In a second, large-scale study (746 patients undergoing exclusively center-based NIHD), propensity score–based matching was used for a retrospective comparison of mortality in patients undergoing NIHD versus those undergoing conventional hemodialysis (28). The mortality at 2 years was significantly lower under NIHD (19% vs. 27%, HR 0.69, 95% CI 0.58–0.84). Switching from conventional dialysis to NIHD lowered the serum phosphate level significantly (from 5.73 to 5 mg/dL) (28).

Similarly, in a retrospective observational study, Bugeja et al. reported that switching to NIHD lowered the phosphate level (median 4.4 vs. 5.3 mg/dL, range 3.8–6.7 vs. 4.3–7.5 mg/dL) (29). The average number of tablets of antihypertensive medication taken daily was lowered from 2 to 1.5, while the average number of phosphate binder tablets taken daily was lowered from 6.2 to 4.9. Quality of life improved during NIHD (29).

The authors established the concept of center-based NIHD for children and adolescents in their own dialysis center in 2005 (30). Twenty-one children and adolescents have been followed to date in an observational study. Switching from conventional hemodialysis to NIHD lowered these patients' requirement for phosphate binders while also lowering their serum

TABLE 4

Figures specific to children and adolescents undergoing intensified hemodialysis

	Reference	No. of pts.	Growth	BMI (kg/m ²)	Puberty	Days absent from school in 6 months
Short daily hemodialysis	Fischbach et al. (25)	5	catch-up of growth in the single prepubertal patient (+1.5 SD in 2 years)	increase by 2.8 ± 0.7 at 1 year	the single prepubertal patient underwent puberty (uterus length +14 mm in 2 years)	fewer (no figures given)
	Fischbach et al. (26)	15	increase of growth rate from 3.8 ± 1.1 cm/year to 14.3 ± 3.8 cm/year	increase from 16.5 ± 2.0 to 18.0 ± 2.4	ns	ns
Nocturnal intermittent hemodialysis	Hoppe et al. (30)	16	ns	increase from 18.2 [15.3–26.8] to 21.2 [14.8–27.1]	ns	decrease from 37 to 12
Nocturnal hemodialysis every night	Geary et al. (33)	4	ns	ns	ns	fewer (figures available for some, but not all, patients)

BMI, body mass index; ns, not studied

phosphate levels (median 1.4 vs. 2.1 mg/dL, range 1–3.6 vs. 0.5–3.6 mg/dL). Two patients had left ventricular hypertrophy under conventional dialysis that regressed after the switch to NIHD. The patients' requirement for antihypertensive medication was also lower. Absences from school became rarer (12 vs. 37 days in 6 months) and quality of life improved (30).

Nocturnal hemodialysis every night

Nocturnal hemodialysis every night is performed for 6–8 hours, 5–7 days a week, almost always at home. This method is most often used in countries with a low population density where patients would have to travel great distances to a dialysis center, e.g., Canada and Australia (17).

In a small-scale prospective randomized trial, 45 patients undergoing nocturnal hemodialysis every night at home were compared with 42 undergoing conventional hemodialysis at home (17). Two primary combined endpoints were chosen: regression of left ventricular hypertrophy or death, and improved health-related quality of life or death (12 months of follow-up). No difference between the two groups was found with respect to either of the endpoints. Patients undergoing nocturnal hemodialysis every night had lower serum phosphate levels and required less antihypertensive medication (17). The main problems of this trial were the small number of cases and the apparently deficient compliance: 25% of the patients assigned to nocturnal hemodialysis every night underwent fewer than 5 dialysis sessions per week. This is the only study in which hemodialysis was carried out at home in both groups.

In the studies to be discussed below, no distinction was drawn between home- and center-based dialysis.

In another prospective randomized trial (conventional hemodialysis vs. nocturnal hemodialysis every

night), patients being treated with intensified hemodialysis experienced a significant regression of left ventricular mass (15.3 g, 95% CI 1.0–29.6 g) (31). Their overall quality of life did not improve, but improvement was seen in certain specific domains (stress due to renal disease). They used less antihypertensive medication and less phosphate-binding medication than patients undergoing conventional hemodialysis (31).

Bergman et al. reported that, in a group of patients who were switched from conventional dialysis to nocturnal dialysis every night, the rate of hospitalization dropped from 0.5 (± 0.15) to 0.17 (± 0.06) admissions per person-year (32). The patients' mean serum phosphate level dropped from 1.7 (± 0.1) to 1.3 (± 0.1) mg/dL.

In 2002, Geary et al. established a program for nocturnal dialysis every night at home for children and adolescents (33, 34). After the switch from conventional hemodialysis, these patients were no longer under fluid or dietary restrictions. Their serum phosphate and PTH levels were markedly lower. These encouraging results are not very informative, however, as only 4 patients were studied (33, 34).

Evaluation of the individual techniques

It is difficult to compare the various techniques of intensified hemodialysis with each other because of the heterogeneity of patient groups and clinical endpoints in the studies performed to date.

The dietary restrictions that are necessary for patients undergoing conventional hemodialysis can often be eliminated with intensified hemodialysis; this is true both for adults and for children and adolescents. Studies in which phosphate homeostasis was investigated revealed an improvement of hyperphosphatemia and/or a lesser need for phosphate binders

(16–18, 20, 28–30, 32, 33). Hyperphosphatemia is a major risk factor for cardiovascular complications.

Arterial blood pressure and/or the need for antihypertensive medication was lowered in all studies in which these variables were investigated (16–18, 22, 28–30, 35). Left ventricular hypertrophy, a surrogate parameter for the risk of cardiovascular death, regressed in 4 of the 5 relevant case series and clinical studies (16–18, 30, 31).

The available studies do not tell us definitively whether intensified hemodialysis improves quality of life. Health-related quality of life improved in only one of the four prospective controlled trials performed to date (16). In the study on NIHD, quality of life remained the same under NIHD, but deteriorated under conventional hemodialysis (18). In one of the studies on nocturnal hemodialysis every night, some domains of quality of life were found to have improved (31); in another, no such difference was detected (17).

Notably, many of the patients undergoing high-frequency intensified dialysis (either short daily hemodialysis or nocturnal hemodialysis every night) switched over to conventional dialysis, or else underwent dialysis at a lower frequency than intended (16, 17, 31). Patients being treated with these methods also had more complications involving vascular access (technical failures) (16, 17). Thus, the high-frequency intensified dialysis techniques may be less useful for many patients over the long term.

The available studies do not definitively answer the question whether intensified dialysis lowers mortality. There was, indeed, a drop in mortality in two of the four prospective controlled trials (16, 18), but one trial showed no effect at all (17). When large retrospective studies are considered in addition, the overall evidence appears inconsistent. Mortality under NIHD was lower than under conventional hemodialysis (28). Short daily dialysis was associated with lower mortality in the study of Kjellstrand et al. (21), but with higher mortality in that of Suri et al. (24).

KEY MESSAGES

- Conventional hemodialysis inadequately compensates for the serious consequences of chronic renal insufficiency.
- Intensified hemodialysis is performed as short daily hemodialysis, nocturnal intermittent hemodialysis, or nocturnal hemodialysis every night.
- Intensified hemodialysis techniques lower arterial blood pressure, improve left ventricular hypertrophy, and lessen patients' need for medications.
- The patients' quality of life and prospects for rehabilitation improve to the greatest extent with intermittent nocturnal hemodialysis.
- Further prospective studies are needed to determine the effect (if any) of intensified dialysis on mortality.

Overview

For patients with end-stage renal failure, intensified dialysis techniques are an option to be considered. Realistically, these techniques can only be carried out at home or else in a specialized center offering nocturnal hemodialysis. Certain psychosocial aspects of intensified hemodialysis may improve patients' prospects for rehabilitation, e.g., improved drug compliance and the opportunity for young patients under nocturnal dialysis to have a normal everyday life at school and at work.

Conflict of interest statement

Prof. Pommer has received reimbursement of scientific meeting participation fees from the Amgen company as well as lecture fees from the Baxter, Fresenius, and Amgen companies. He is a member of the German Dialysis and Renal Transplantation Board (*Kuratorium für Dialyse und Nierentransplantation*). Dr. Thumfart, Prof. Querfeld, and Prof. Müller state that they have no conflicts of interest.

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