Abstract. There is evidence that high frequency, as well as long duration, hemodialysis provides better clinical outcomes. We developed nocturnal hemodialysis, a new innovative form of renal replacement therapy, which is performed six to seven nights per week for 8 to 10 h during sleep at home. Blood flow was set at 300 ml/min and dialysate flow at 100 ml/min. An internal jugular catheter was used as the vascular access. Special precautions were taken to prevent accidental disconnection during sleep, as well as air embolization. Dialysis functions from the patient's home were monitored continuously via a modem at the nocturnal hemodialysis center. Twelve patients have completed training and have been successfully performing nocturnal hemodialysis for up to 34 mo. This study represents 170 patient months of experience accumulated over 3 yr.

The number of patients starting on dialysis every year has been increasing by 10% with significant impact on the cost of delivery of treatment to patients with end-stage renal disease (1). Limitations in the use of continuous ambulatory peritoneal dialysis (CAPD) will increase the need for hemodialysis with significant financial implications (2,3). At the same time, there is significant evidence that increasing dialysis dose leads to a decrease in morbidity and mortality, creating the need for more effective forms of dialysis (2,4–8). Although home hemodialysis has been associated with better outcomes, its prevalence has been steadily declining (9). Impressive results of patient survival have been associated with long duration (5) as well as high frequency hemodialysis (10). Nocturnal hemodialysis combines high frequency, long duration, and low cost with high level of patient satisfaction. In this article, we are present a detailed description of the method, as well as the experience accumulated over 3 yr.

Materials and Methods

Patients

Eligibility Criteria. Eligibility criteria were liberal. Subjects for the study were selected from a pool of 160 patients. The main criteria were willingness to participate and capability to be trained for home hemodialysis. Motivating factors for enrollment included large body size in one patient, significant cardiovascular disease and ineligibility for kidney transplantation in a young diabetic patient, and eagerness to return to full-time employment in two patients. Exclusion criteria included perceived inability to be trained for home hemodialysis or inappropriate housing. The primary limiting factor for patient recruitment was available funding for the demonstration project, rather than available patients. At this early stage, ability to speak English was necessary so that patients could communicate with program observers at night. Each patient selected for this study was stable. Patients with comorbid conditions were not excluded. Long distance from the dialysis center was not a contraindication. Presence of a “partner” for hemodialysis was not required.

Training. Training was done 3 d per week for 4 to 6 wk on an outpatient basis, depending on previous experience with self-care or home hemodialysis. Except for the last week, the patients were maintained on conventional hemodialysis 3 times per week. At the end of training, each patient carried out nocturnal hemodialysis for six consecutive nights in the nocturnal hemodialysis center before going home. Training of patients was done by a dedicated research hemodialysis nurse. During the past year, five more nurses have been trained for this purpose. The length of the training for a nurse with previous experience in home hemodialysis training was 1 to 3 d. Training material was written by the research nurse, and patients received a copy of the training manual.

Methods

Description of the Dialysis Procedure. Nocturnal hemodialysis involved hemodialysis at home for 8 to 10 h, while asleep, for six to seven nights per week. All patients run a blood flow of 250 to 300 ml/min. A low surface area (0.7 m²) polysulfone dialyzer was used.
(Fresenius F40, Fresenius Medical Care, Lexington, MA). Dialysate flow of 100 ml/min was used for all patients. Recently, we used dialysate flows of 200 ml/min in selected patients and even 300 ml/min in two patients with large body size. The results reported in this article were collected while on dialysate flow of 100 ml/min. The blood flow was maintained at a relatively high rate to decrease the potential for clotting of the dialysis catheter. Low dialysate flow was initially chosen to limit the dialysis clearance per hour to avoid possible complications related to excessive dialysis. Anticoagulation was achieved with heparin, at an average hourly rate of 1100 ± 300 U/h. No heparin bolus was administered, except for the residual heparin left in the limbs of the catheter when the heparin was withdrawn before initiation of dialysis. Heparin was withdrawn only partially so no blood entered into the syringe, to prevent blood loss. The dose was adjusted to the needs of the patients, based on clinical evidence of clotting of the extracorporeal circuit. All patients were dialyzed using dialysate containing potassium at 2 mEq/L and bicarbonate at 28 to 32 mEq/L. Although initially the dialysate calcium concentration was kept at 1.25 mmol/L, it was later raised in most patients. This change was adopted to prevent negative calcium balance during dialysis in patients who required higher serum calcium to suppress parathyroid hormone (PTH). Because the patients at entry to the program had varying degrees of secondary hyperparathyroidism and required different serum concentrations of calcium, we have recently adopted the following approach. Calcitriol was started in the patients with elevated PTH at doses high enough to achieve suppression of the hormone. The patients were trained to add calcium chloride powder into the acid concentrate. The dose was titrated so that the postdialysis serum calcium was slightly higher than the predialysis calcium. This prevented negative calcium balance during dialysis. Obviously, patients in whom serum calcium is kept high to suppress PTH require a higher dose of dialysate calcium. Thus, the dialysate concentration of calcium was individualized.

Vascular Access. Vascular access was achieved via a long-term internal jugular catheter developed by this group (Uldall Cook catheter) and manufactured by Cook Critical Care (Bloomington, IN). A locking box was designed (Figure 1) to prevent accidental disconnection of the dialysis line from the catheter. This effectively prevented physical separation of the blood lines from the catheter limbs. We also adopted the InterLink® system (Becton Dickinson, Franklin Lakes, NJ) to prevent bleeding and air embolism during the process of connection and disconnection from the dialysis tubing (Figure 2).

Dialysis Machine. A Fresenius 2008H dialysis machine was modified by the manufacturer to produce a dialysate flow of 100 ml/min (6 L/h). The revision was subsequently incorporated into the currently commercially available machines.

Water Treatment. At the early phase of the study, a deionizer at the home of the patient was used to provide water treatment. It was chosen over a reverse osmosis system for its quiet operation. Recently, we have been using reverse osmosis systems, which are easier to sterilize.

Remote Monitoring. All of the main dialysis functions displayed on the front panel of the Fresenius machine have been monitored remotely each night, via a modem, on the computer screen in the nocturnal hemodialysis office. Initially, a computer with the Fresenius FDS08 computer software was installed at the home of the patient and the information collected was transmitted to the center, using the pcAnywhere® software (Symantec Corp., Cupertino, CA). An overnight observer polled, every few minutes, one home computer at a time. During the past 9 mo, we have been using the DAX® dialysis software (Cybernius Medical, Edmonton, Alberta, Canada). The dialysis machines at home were connected to the Wellesley Central Hospital via a modem without the need of a computer or software at the home of the patient. This system allowed continuous "live" simultaneous monitoring of all patients on a single screen. A visible and audible alarm alerted the observer if there was a dialysis machine alarm. If the patient did not correct the problem within a few minutes, the observer called the patient through a second telephone line. If the patient was unable to resolve the problem, the observer contacted the registered nurse, technologist, or physician on call. If necessary, the patient terminated the dialysis process for the night. No emergency

Figure 1. Locking box preventing accidental disconnection of the blood tubing from the Uldall Cook catheter.
visits by the technical personnel were necessary. The observers did not have prior knowledge or training, but they were trained by the research team. Detailed information of the frequency and the cause of alarms, as well as the compliance of nine patients for 3 consecutive months, was reviewed.

Dialyzer Reuse. To decrease the cost of dialysis, dialyzer reuse was organized. We have established a system of transportation of the used and rinsed dialyzers to the Wellesley Central Hospital, where they are reprocessed. The patients rinsed their dialyzers with heparinized saline at the end of dialysis and stored them daily in a small refrigerator. Once a week, they visited the closest laboratory of a collaborating network of laboratories (MDS Laboratories). They exchanged their properly labeled, used dialyzers for a set of already processed dialyzers stored in the laboratory. The dialyzers were then transported to the hospital for reprocessing. Dialyzers were reprocessed by an automated Renatron system using Renalin®. Dialyzers were rejected if the dialyzer volume decreased by more than 20% or failed the other standard tests.

Evaluation of the Method

Dialysis Adequacy. We collected serum and all spent dialysate for three consecutive conventional hemodialysis sessions, for 1 wk before the conversion to nocturnal hemodialysis and nightly for 1 wk after the conversion for measurement of urea, creatinine, phosphate, and $\beta_2$ microglobulin. $\text{Kt/V}$ was calculated from the serum and collected dialysate urea (11). While on conventional hemodialysis, the patients underwent dialysis 3 times a week on a Fresenius 2008H machine for 4 h using 1.8-m$^2$ polysulfone dialyzers (Fresenius F80) and a dialysate containing 40 mEq/L bicarbonate. Calcium concentration was 1.25 mmol/L, and K concentration was 1 or 2 mmol/L. Blood flow was maintained at 401 ± 91.6 ml/min and dialysate flow at 514 ± 10.9 ml/min. Urea, creatinine, and phosphate were measured by a multianalyzer (Ektachem 500; Eastman Kodak Clinical Diagnostics, Rochester, NY). The $\beta_2$ microglobulin concentration was determined by microparticle enzyme immunoassay (IMX system; Abbott Laboratories, Abbott Park, IL).

Nutrition. Body weight, serum albumin, and protein were followed. Protein intake was also followed prospectively from dietetic records, which the patients kept for 3 d every 6 mo.

Other Parameters. BP control, number of antihypertensive medications, hemoglobin response, and erythropoietin (EPO) dose were followed.

Statistical Analysis

Values were expressed as mean ± SD. Paired $t$ test was used for comparisons of means.

Results

Patient Training

From April 1994 to January 1997, 13 patients were considered for training. In one patient, the training was terminated before conversion to nocturnal hemodialysis because he was considered unsuitable to continue. Twelve of the patients completed the training. Of the 12 trained patients, one was removed from the program 3 mo later because of poor adherence to the dialysis technique. One of the patients was transplanted 18 mo later, and 10 patients continued on the program. Eleven patients were trained to perform dialysis independently, and one patient and his spouse functioned as a team. Although the patients were allowed to skip dialysis one night a week, three of the 12 patients elected to dialyze nightly because they felt better. The group of 12 patients has been on nocturnal hemodialysis for 3 to 34 mo, with a mean of 15.6 mo. Altogether, there has been a 170 patient-month experience as of January 1997. Laboratory results of the first 11 patients are reported in this article.

Patient Characteristics

Of the 12 trained patients, four were women and eight were men. There were two diabetic patients. The age of the patients was 40 ± 10 yr (range, 30 to 65 yr). The etiology of renal failure was diabetes in two patients, chronic glomerulonephritis in three, reflux nephropathy in one, polycystic kidney disease in two, hypertensive nephrosclerosis in one, and unknown in two. One patient is paraplegic due to tropical paraparesis. The patients had been in end-stage renal disease for 8.29 ± 7.54 yr. One patient lives alone, two live with young children, and the rest live with adult family members.

Tolerance of the Method

The patients adapted easily to the dialysis and slept without difficulty; some even reported improvement in their sleep pattern. The adaptation period lasted for less than 1 wk. The alarms during the night have not interfered significantly with the patients’ sleep, with the exception of one patient. She had restless sleep with a significant number of alarms, necessitating that the number of nights on dialysis be decreased to 4 per week. Recently, after replacement of her dialysis catheter, the frequency of the alarms has decreased. Sleep studies were done in all patients before and after the conversion to nocturnal hemodialysis. The data are currently being analyzed.

In a review of data collected during 3 consecutive months, the mean frequency of dialysis per week varied from 4 to 7 times (5.69 ± 1.10). One patient had frequent alarms and chose to be dialyzed only 4 times per week. The mean duration of dialysis was 8.91 ± 0.65 h per night. The mean number of

Figure 2. The InterLink® system (Becton Dickinson) prevents air embolism and bleeding from the dialysis catheter.
Vascular Access
All of the patients have achieved the desirable blood flows of 250 to 300 ml/min. Although this flow rate is higher than required for urea equilibration between serum and dialysate, it was chosen to prevent clotting. No studies have been done to substantiate the need for these higher blood flows.

Technical Aspects
Dialyzers were reused on average 5.09 ± 3.92 times. Recently, we switched to Fresenius F50 dialyzers, expecting an increase in the number of reuses. Lack of a higher number of reuses is probably related to the delay of reprocessing.

Hemodynamic Stability
Ultrafiltration during the prolonged dialysis was very well tolerated. During the first week of nocturnal hemodialysis while in the hospital, BP measurements indicated that the BP was stable. Postdialysis hypotension (systolic BP, <100 mmHg) was encountered in a small number of cases, necessitating a decrease in the dose of antihypertensives or an increase in the target weight. Routine BP measurements were avoided during dialysis because they would disturb the patients’ sleep. An hourly ultrafiltration rate of 400 ml/min has been arbitrarily imposed as the highest rate allowed. This allowed the removal of up to 4.0 L of fluid nightly, which was adequate for all of the patients. Higher rates are likely to be as well tolerated but were not required up to this point. Decrease in intravascular volume during dialysis was well tolerated, and patients who had frequent symptoms on conventional hemodialysis became asymptomatic. On three occasions, patients reported postdialytic cramping, which improved with an increase of target weight. Target weight was increased either at the request of the patients or because of a decrease in BP despite discontinuation of antihypertensive medications. Often, target weight was decreased to achieve BP control and decrease the need for antihypertensive medications, despite the lack of clinical evidence of intravascular volume expansion. The relative lack of symptomatology from a decrease in intravascular volume during dialysis occasionally led to a delay in the adjustment of the target weight. No dialysis disequilibrium symptoms were encountered during nocturnal hemodialysis, even when dialysate flows of 300 ml/min were used.

Clinical Response to Nocturnal Hemodialysis
Most patients reported greatly enhanced energy and well being. They were enthusiastic about the improvement in most of their preexisting symptoms. Pruritus, nausea, postdialytic symptoms, and lack of energy decreased or disappeared. Appetite increased in most patients and their diets became liberal. Three male patients gave an unsolicited report of an increase in libido.

Biochemical Control
Urea. There was no urea rebound after nocturnal hemodialysis. Serum predialysis urea progressively decreased, and there was a smaller fluctuation of the levels pre- and postdialysis. The mass of the urea removed daily decreased, and a new equilibration was achieved after the second dialysis session. The dialysate urea during the three conventional and six nocturnal hemodialysis sessions is depicted in Figure 3. After equilibration, the mass of the urea removed per nocturnal hemodialysis session was about half of the amount removed by a conventional hemodialysis session, and the total weekly urea removed by the methods were similar (1856 ± 413 versus 1636 ± 301 mmol; P = 0.13). Kt/V per hemodialysis session (calculated from collected dialysate) during conventional hemodialysis at 1.26 ± 0.29 was higher than nocturnal hemodialysis at 0.99 ± 0.3, but obviously the weekly Kt/V on nocturnal hemodialysis was almost double, depending on the frequency of dialysis per week (six or seven nights). Figure 4 depicts the pre- and postdialysis urea on conventional and nocturnal hemodialysis during the first week after the conversion. Monthly serum pre- and postdialysis urea levels 3 mo before the conversion and for 1 yr on nocturnal hemodialysis are depicted in Figure 5.

Creatinine. Serum creatinine levels followed a pattern similar to the urea levels. Although the mass of the creatinine removed per session was higher on conventional hemodialysis, the mass of creatinine removed weekly was not different between the two methods (63.75 ± 31.78 versus 60.04 ± 44.16 mmol; P = 0.62). Creatinine levels pre- and postdialysis for 3 mo before the conversion and for 1 yr on nocturnal hemodialysis are shown in Figure 6.

Phosphate. The mass of the phosphate removal during each session of nocturnal hemodialysis was similar to the amount removed during each session of conventional hemodi-
Figure 4. Serum urea pre- and post-CHD and pre- and post-NHD.

Figure 5. Serum urea pre- and posthemodialysis on CHD and NHD.

Figure 6. Serum creatinine pre- and posthemodialysis on CHD and NHD.

Figure 7. Total dialysate phosphate per session of CHD and NHD.

Figure 8. Serum phosphate pre- and postdialysis on CHD and NHD.

Figure 9. Serum phosphate pre- and postdialysis on CHD and NHD.

Figure 10. Serum phosphate pre- and postdialysis on CHD and NHD.

Nocturnal Hemodialysis

Serum urea pre- and post-CHD and pre- and post-NHD. The weekly phosphate mass removal was approximately twice as high during nocturnal hemodialysis at 150 ± 47 versus 82 ± 22 mmol (P = 0.0006). Serum predialysis phosphate decreased to normal levels, and all patients were off all calcium carbonate used as a phosphate binder (median dose, 2.4; range, 1.4 to 4.5 g/d) within 1 to 4 wk of nocturnal hemodialysis. After the first month on nocturnal hemodialysis, 10 of 12 patients had frequent low phosphorus values postdialysis. In eight patients, the postdialysis phosphate was intermittently below 0.6 mmol/L. Two patients required phosphate supplements in the form of Phosphate Sandoz® (250 to 500 mg) once every night on a long-term basis. The supplements were given at night, before retiring, to prevent high serum phosphate predialysis and postdialysis hypophosphatemia. Phosphate levels pre- and postdialysis for 3 mo before the conversion and for 1 yr on nocturnal hemodialysis are shown in Figure 8.

β₂ Microglobulin. The mass of β₂ microglobulin removed per session of nocturnal hemodialysis was twice as high as on conventional hemodialysis, and thus the weekly removal was approximately 4 times as high as on conventional hemodialysis (52.13 ± 10.6 versus 12.14 ± 2.09 mmol; P < 0.0001). The dialysate β₂ microglobulin during the three conventional and six nocturnal hemodialysis sessions is depicted in Figure 9. Serum levels of β₂ microglobulin decreased within the first few days on nocturnal hemodialysis and are depicted in Figure 10.

Hemoglobin Levels and EPO Use

Hemoglobin levels remained stable during the first year on nocturnal hemodialysis. Despite early trends, EPO dose did not change significantly. The average predialysis hemoglobin was 101.27 ± 10.19 g/L and remained stable at 12 mo (111.06 ± 17.52; NS). EPO, given subcutaneously at a dose of 11,083 ± 9,040 at the conversion to nocturnal hemodialysis, was unchanged at 9200 ± 9295 U/wk 12 mo later. All patients were on ferrous gluconate orally at a dose of 300 mg 3 times daily
with variable compliance. This regimen was already being used before the conversion to nocturnal hemodialysis. Ferritin levels (56 ± 50 μg/L) and transferrin saturation (0.24 ± 0.13) were low.

**BP Control**

Most patients who were trained on nocturnal hemodialysis were on antihypertensive medications. BP was controlled in all patients. BP pre- and postdialysis is depicted in Figure 11. In nine patients with adequate follow-up, the average number of antihypertensives decreased from 2.67 ± 1.12 while on conventional hemodialysis to 1.78 ± 1.20 at 6 mo and 1.67 ± 1.17 at 12 mo on nocturnal hemodialysis (P = 0.03) (Figure 12). Of 11 patients with more than 6 mo follow-up, 10 were on antihypertensives at the conversion to nocturnal hemodialysis, but only five were on such treatment at the last point of follow-up or exit from the program. Decrease in BP was at least partially related to decrease in extracellular fluid volume. Despite the presence of euvoemia or even hypovolemia, based on physical examination, the target weight was decreased further, resulting in further improvement in BP control. This was tolerated without symptoms in most patients. Temporary transfer of one patient to conventional hemodialysis led to significant increase in the need for antihypertensive medica-

**Nutrition**

There was an increase in appetite in many patients. Although this has led to an increase in body weight in some patients up to 5.5 kg, the overall increase by 1.0 ± 3.0 kg within the first 12 mo was not significant. In three patients, target weight was decreased within the first few months to achieve euvoemia and better BP control. Serum albumin was normal before the conversion to nocturnal hemodialysis at 41.2 ± 2.6 and remained unchanged at 41.4 ± 2.7 g/L. Protein intake as calculated from dietary records increased, within the first 6 mo, from 59 ± 18 to 86 ± 13 g/d (P = 0.004) or 1.0 ± 0.3 to 1.44 ± 0.2 g/kg per d (P = 0.009). Calorie intake did not increase significantly (1550 ± 670 before conversion to 1800 ± 360 kcal/d at 6 mo after conversion).

**Vocational Rehabilitation**

Before the conversion to nocturnal hemodialysis, of the 12 patients, two were retired and two were disabled. Of the eight remaining patients, three were not working, two worked full time, and three worked part time. After conversion to nocturnal hemodialysis, of the eight eligible patients, six were fully employed, one continued to work part-time, and one patient is unemployed seeking employment. In addition to the improved feeling of well being, several of the fully employed patients
ascribed their success to the lack of hemodialysis during the day.

Financial Aspects

On the basis of the known needs of the nocturnal hemodialysis program, we projected that a cost-efficient program should service 30 patients to achieve economies of scale. The cost of consumables, telecommunications, and personnel is calculated at Can $23,000 (Canadian dollars) per patient year. This amount does not include cost for the purchase of the dialysis machine, water treatment, or initial renovations at the home of the patient. This amount includes reprocessing of the dialyzer 6 times and is comparable to the cost of CAPD for four 2-L exchanges per day and only slightly higher than conventional home hemodialysis. This cost may vary significantly in different countries. Detailed prospective financial analysis has not yet been performed. The cost of the remote monitoring depends mainly on the personnel cost (two full-time equivalents), telecommunication costs, and the number of patients monitored simultaneously. In a unit with 30 patients, the approximate cost for remote monitoring would be Can $2000 to $3000 per patient year but would be significantly decreased with increasing number of patients.

Complications

Catheter-Related Complications. Twenty-two catheters were replaced during 186 patient months (one catheter per 8.4 patient months). Six replacements were related to clotting, four to exit-site infection, six to bacteremia, and six to technical problems (kinks, inconvenient position, etc.).

There were 12 episodes of partial or complete catheter occlusion in 11 patients over 186 patient months. In four episodes, infusion of a total of 250,000 U of urokinase into both catheter limbs resolved the problem. Meperidine (Demerol) at a dose of 25 mg was given intravenously before the infusion to prevent adverse reactions. In two episodes, the patency was restored only after a second urokinase infusion. In the other six cases, the catheter was replaced over a guidewire. Ten patients required oral anticoagulants in the form of warfarin on a long-term basis. Oral anticoagulation was instituted with the first episode of catheter clotting or decreased flow. The initial dose was 1 to 3 mg and was not increased even in the presence of subtherapeutic international normalized ratio. Subsequent episodes of clotting in the same patient led to increases in the dose of warfarin. Repeated injections of urokinase were necessary, followed by increases in the dose of warfarin, until the clinically effective level of anticoagulation was achieved. Using this approach, the dose for those on the treatment was $2.1 \pm 1.6$ mg/d, and average international normalized ratio was $1.5 \pm 0.9$.

Six catheters were replaced because of technical problems. These included poor catheter position, inconvenient location of the exit site, and kinking of the catheter in the subcutaneous tunnel. Most of these problems were encountered during the earlier part of the study and were less frequent after a small number of dedicated radiologists were involved in catheter insertions.

Four episodes of exit-site infections in three patients required catheter replacement. Two catheters required replacement over a guidewire. Two catheters were removed and reinserted on the opposite side. Six episodes of bacteremia were encountered in three patients (one episode per 31 patient months). One catheter was changed over a guidewire. The rest were removed and reinserted on the opposite side of the chest. Only one patient was hospitalized.

Gastrointestinal Bleed. Two patients developed gastrointestinal bleed. A patient with cirrhosis bled from a duodenal ulcer. A paraplegic patient bled from colonic ulcers. Both patients were on warfarin. In both cases, the anticoagulation was reversed and the patients were transferred to conventional hemodialysis without heparin for a few weeks. They then returned to nocturnal hemodialysis.

Other. One patient developed low-grade fever of unknown etiology in the evenings, present for at least the past year. Extensive investigations did not disclose the etiology of the problem. During a temporary conversion to conventional hemodialysis for 6 wk, her symptoms were unchanged.

Hospitalizations. Five patients have needed admission to the hospital. Two patients were admitted for gastrointestinal bleed, one for menorrhagia, and one for chest pain. One patient was admitted for dialysis line sepsis after he ignored symptoms related to the infection for several days.

Discussion

Nocturnal hemodialysis was created in response to the need for a well tolerated, efficient, and affordable home dialysis treatment.

Nocturnal hemodialysis provides the highest clearance of any dialysis modality currently in use in chronic dialysis patients. Although the initial data from the National Co-operative Dialysis Study were interpreted as suggesting that a Kt/\( V \) of 1.0 was adequate (12), more recent studies have shown improved survival with increasing dialysis dose, both in hemodialysis and CAPD (2,4–8). Most of the studies did not find any further decrease in mortality in hemodialysis with Kt/\( V \) greater than 1.4, but the authors indicated that the number of patients on higher dialysis dose was not sufficient to identify potential differences (4,8). It is likely that the improvement from further increase in dialysis dose is less significant and more difficult to demonstrate, but is still likely to exist. The much higher dose provided by nocturnal hemodialysis will allow a reevaluation of the question of optimal dialysis dose. The higher clearance on nocturnal hemodialysis is related to the duration of dialysis, which is dictated by the length of sleep of the patients. Decreasing the length of dialysis obviously would not be practical or serve any purpose. Furthermore, there is no excessive financial burden by the lengthy dialysis, especially in the presence of low dialysate flow. It is likely that better clearance, closer to the kidney function, will be advantageous not only in terms of mortality but also uremic symptomatology and improvement in the function of the multiple organ systems affected by uremia. Nocturnal hemodialysis allows patients with large body weight to receive the appropriate prescription by increasing the dialysate flow to 200 or 300 ml/min. Further
increases in the dialysate flow is unlikely to be necessary. Thus, nocturnal hemodialysis provides a solution to the increased dialysis needs of patients with large body size.

A significant advantage of nocturnal hemodialysis is the length of dialysis. It offers at least 4 times the length of a typical 4-h hemodialysis. Dialysis duration has been considered a significant factor for improved morbidity and mortality (13,14). Impressive survival results were reported from Tassin, France. These results have been linked to the long duration of dialysis, although there also was an associated high Kt/V of 1.7 per dialysis session (13). Nocturnal hemodialysis offers twice the duration of dialysis offered by the Tassin group. Increased length of dialysis has several advantages: (1) it provides hemodynamic stability even in patients with an unstable cardiovascular system; (2) it allows smoother adjustment of the patient's target weight without symptoms of intravascular volume contraction; (3) it potentially improves BP control (15); and (4) it enhances the clearance of middle molecules.

Nocturnal hemodialysis is also advantageous because of its high frequency. Daily hemodialysis offers significant advantages. It is more physiologic (16) in that it decreases the fluctuations of the levels of the waste products. Daily dialysis further enhances the hemodynamic stability and allows a more liberal food and fluid intake. Significant experience in Italy with daily short hemodialysis has demonstrated improvement of well being, lower BP, improved cardiovascular control, decreases in cardiac hypertrophy, and improvement in libido (10,17). Daily short hemodialysis would not be expected to offer the increased clearance of middle molecules of the longer dialysis regimens. Nocturnal hemodialysis combines the advantages of short daily hemodialysis and long duration dialysis. Casino and Lopez (18) introduced the concept of equivalent renal urea clearance (EKRe) to enable comparison of different dialysis modalities. EKRe for conventional hemodialysis in our patients was estimated at 14 ml/min. Nocturnal hemodialysis six nights a week offers EKRe of 22 and 27 ml/min at six and seven nights a week, respectively. Dialysate flows greater than 100 ml/min obviously would offer higher clearance. Urea modeling does not address the potential benefits from the long duration of dialysis.

Low dialysate flow was chosen as a limiting factor of the intensity of dialysis. Concerns that a prolonged efficient nightly dialysis may not be well tolerated or lead to deficiency syndromes led to the decision to limit the intensity of dialysis. Subsequently, the dialysate flow was increased in several patients without sequelae. The blood flow was maintained at 300 to 350 ml/min. Although this flow is not necessary, it was hoped that it would lead to less frequent clotting episodes.

The tolerance of the dialysis procedure has been excellent. BP of patients was very stable during dialysis, and no significant BP drop was recorded during dialysis during the first week while in the hospital or postdialysis during the entire period of follow-up. During almost 3 yr of nocturnal hemodialysis, no episode of hemodynamic instability was experienced that would require the presence of a "helper." No significant postdialytic symptoms have been experienced, and the patients are well rested after dialysis. Patients with high intradialytic weight gain and postdialytic symptoms while on conventional hemodialysis have improved. Fluid removal has been achieved without difficulty. Ultrafiltration rates up to 400 ml/h have been tolerated without difficulty. Experience with higher rates has not yet been gained.

Phosphate control has been excellent during nocturnal hemodialysis. Oral phosphate supplements were necessary, and after the end of the reported part of the study, addition of phosphate into the dialysate has been instituted (19).

Weekly $\beta_2$ microglobulin removal is 4 times higher than conventional hemodialysis. This is not unexpected because the length of nocturnal hemodialysis is 4 times longer than that of conventional hemodialysis. At this point, it is difficult to predict the impact of this improved removal on the development of dialysis-related amyloidosis. The effect of dialyzer reuse on $\beta_2$ microglobulin clearance has not been studied.

All patients are on a dialysate containing potassium at 2 mEq/L. Despite the liberal diet, they have maintained normal serum potassium. Of course, the dialysate potassium can be adjusted to accommodate the patients' needs, although up to this point, we have not had to adjust the dialysate potassium in any of our patients.

The BP of all patients is well controlled. The number of antihypertensive medications necessary decreased significantly. Successful BP control has been reported with long hemodialysis (15) and daily short hemodialysis (17). Despite the better BP control, some of our patients still require antihypertensives. The difference, compared with the reported excellent results of the Tassin group (13) in which no medications were necessary, could be related to different patient selection or possibly to a more aggressive decrease in the target weight of the patients in Tassin.

Control of anemia has been associated with higher dialysis dose (20). Despite early trends, we have not seen a significant decline in the dose of EPO. This may have been related to excessive blood loss due to the daily schedule of the treatment and the lack of treatment with intravenous iron. Recently, all patients were started on intravenous iron saccharate (Venofex®; Vifor International, St. Galen, Switzerland), administered by the patients at home.

No conclusions can be drawn at the present time regarding the effect of nocturnal hemodialysis on renal osteodystrophy. It is expected that the excellent phosphate control would help in the prevention of secondary hyperparathyroidism. Furthermore, maintaining high enough serum calcium to suppress PTH is possibly without significant risks, in view of the excellent control of serum phosphate. There are several theoretical concerns that need to be addressed. High phosphate clearance could lead to osteomalacia. The lack of need for calcium supplements as phosphate binders may lead to negative calcium balance, which may be prevented using high dialysate calcium and oral calcitriol administration. The effect of prolonged treatment with heparin on the bones is unknown. Finally, better dialysis and good phosphate control could decrease the resistance of bones to PTH leading to osteitis fibrosa in patients who already have very high PTH levels at the time of the conversion to nocturnal hemodialysis.
Although the data from quality-of-life questionnaires have not been analyzed, the patients on nocturnal hemodialysis have expressed high satisfaction with their subjective improvement. Their levels of energy and stamina have improved immensely. Other favorable outcomes are related to their decreased number of medications, unrestricted diet, and freedom provided by the dialysis at home, performed at a time that leaves the entire day open to pursue other activities. We have noted that several patients returned to full-time employment; the need to do so was the motivating factor for the choice of this dialysis modality.

Because nocturnal hemodialysis is a form of home dialysis, it is less costly than in-center dialysis. Dialyzer reprocessing has rendered the cost of this modality equal to the cost of CAPD (four 2-L exchanges per day). Furthermore, it has allowed the choice of high-flux dialyzers, with their anticipated advantages (21), without increasing the cost of the method. The training of patients on nocturnal hemodialysis is obviously more expensive due to the duration of the training, akin to training for home hemodialysis.

The hospitalization rate of patients on dialysis and the associated costs are very high (22). In 1991, $2.2 billion was spent on inpatient care in the United States. Increased dialysis dose from Kt/V of 0.82 to 1.33 caused a reduction of the gross annual mortality rate from 22.8 to 9.8% (6). Furthermore, the hospitalization rate fell from 15.2 d/patient per yr to 10.3 d/patient per yr. It is anticipated that improved dialysis using nocturnal hemodialysis will decrease the hospitalization rate and decrease the cost of care of these patients. Further savings will be realized through decreased medication costs (antihypertensive medications, phosphate binders, possibly EPO). Improved quality of dialysis is expected to improve patient survival. Comorbidities, especially coronary artery disease and diabetes, are significant factors leading to increased morbidity and mortality (23,24). Hemodynamic stability is a significant factor for prevention of complications. Nocturnal hemodialysis offers the best hemodynamic stability of all of the outpatient hemodialysis regimens and is likely to offer extra benefits over and above the benefits related to high dialysis dose. Furthermore, hemodynamic stability may have a stabilizing effect on the residual kidney function.

Patients on nocturnal hemodialysis are monitored nightly, through a computer connection. We have taken all the necessary safety measures to prevent serious complications, such as accidental disconnection of the catheter and air embolism. Still, because there is a significant probability that the patients may not be awakened by the machine alarms, we believe that at this point there is a need for remote monitoring. Furthermore, we are able to ensure that the patients are complying with the recommended dialysis. Finally, through the remote monitoring, better collection of data is possible. However, remote monitoring is not essential for nocturnal hemodialysis. The worse-case scenario, which can be addressed by remote monitoring, is that lack of attention to an alarm by the patient would lead to clotting of the extracorporeal circuit. We do not think that accidental disconnection is possible with the current connection techniques. Furthermore, significant bleeding or air embolism during sleep would result in acute emergencies, which could not be possibly affected by the remote monitoring. After the completion of this study, we established a remote connection via the Internet. Through a local Internet provider, a computer at the home of the patient, connected to the dialysis machine, was able to transmit data to a server located at the nocturnal dialysis center, also connected to the Internet. The advantage of the Internet connection was that it obviated the need for long-distance telephone connections and decreased the communication costs. The ability to monitor patients over the Internet would allow the creation of centers for monitoring entire regions, thus achieving economies of scale.

Malnutrition is a common problem in patients on maintenance dialysis. The dialysis procedure is a strong catabolic stimulus for hemodialysis patients, and protein loss in the peritoneal dialysate is a risk for protein malnutrition (25,26). Increased dialysis dose has been associated with improved appetite and increased PCR. Follow-up of the nutritional status of the patients on nocturnal hemodialysis will help establish the dialysis dose, which achieves the full correction of malnutrition in dialysis patients. We found an increase in the protein intake on nocturnal hemodialysis. Some of the patients have gained significant weight (up to 5.5 kg), whereas in others the target weight was decreased significantly to correct the preexisting state of extracellular volume expansion or achieve better hypertension control. A significant concern was the anticipated loss of water-soluble nutrients with increased dialysis. We increased the daily dose of the multivitamin preparation, although we have no evidence that this was necessary. No specific deficiency syndromes were identified.

The complication rate was low and has not affected the treatment significantly. The Uldall-Cook catheter has been used exclusively. We avoided using fistulas or grafts for fear of accidental disconnection during the night. Further research is necessary for development of a safe peripheral access for nocturnal hemodialysis. Ideally, peripheral arteriovenous fistulae and grafts should be used for nocturnal hemodialysis. For this to be achieved on a routine basis, the problem of the firm attachment of the dialysis tubing to the access needs to be resolved. Although we did not encounter any clinically apparent case of large vein stenosis in our patients, the long-term use of in-dwelling catheters should be addressed. Nightly long heparinization may be protective in these patients, and the increased dialysis efficacy may confer other benefits in relationship to the long-term patency of the veins by decreasing hypercoagulability associated with uremia (27,28). More experience is needed to draw definite conclusions.

In the interim, we are expanding the nocturnal hemodialysis program to 30 patients, which we think will provide economies of scale. The Ministry of Health of Ontario has funded this expansion. In view of the significant success of this project, we expect dissemination of the method. Sharing resources between programs will help alleviate the costs related to remote monitoring of the patients.
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References