Clinical outcomes have not improved substantially for patients treated with conventional thrice weekly hemodialysis. More intensive hemodialysis regimens, including daily short dialysis, and nocturnal prolonged dialysis show promise to improve morbidity and mortality. Published studies and trials underway examining these therapies are reviewed.

**Thrice Weekly Prolonged Hemodialysis**

More than 25 yr ago, Charra and colleagues from Tassin, France, first published their experience with thrice weekly long duration, slow flow hemodialysis (5). Patients were treated with low salt diet, long, slow dialysis and focused efforts to return total body volume to normal. Initial and follow-up studies (6) over many years showed impressive volume control, BP control without use of many antihypertensive medications and remarkable survival. Despite these findings, dialysis in the United States moved toward shorter rather than longer treatments. When higher surface area dialyzers accelerated small molecule removal, and use of urea-based measures of dialysis adequacy became standard, hemodialysis treatments times were reduced. Few centers in the world followed Dr. Charra’s lead in offering prolonged dialysis treatments. In recent years, Charra’s basic technique has been adapted to create in-center nocturnal hemodialysis (INHD), delivering thrice weekly overnight treatments lasting 6 to 8 h with reduced blood pump speeds of about 300 ml/min. Such prolonged dialysis allows for more gradual ultrafiltration, an improvement in dialysis that might be expected to improve patient survival (7). Troidle and colleagues (8) reported results in 16 patients switched from conventional to INHD. Kt/Vurea rose from 1.2 ± 0.16 to 2.6 ± 0.65 and the ultrafiltration rate fell from 10.3 ± 4.5 to 5.9 ± 1.7 ml/h/Kg. Despite the need to spend three nights a week sleeping in a dialysis facility, INHD patients had no measurable change in psychosocial assessments. Phosphorus levels fell from 5.3 ± 1.3 to 4.4 ± 1.1 mg/dl. In another study from Toronto, Bugeja et al. switched 39 patients from conventional to 8-h INHD (9). They also found increased urea removal (urea reduction ratio increased from 74% to 89%) and improved phosphorus control (phosphorus fell from 5.9 to 3.7 mg/dl). Patients required fewer antihypertensive medications to control BP, and lower doses of erythropoesis-stimulating agents to treat anemia. Quality of life, as assessed with a ten-point Likert scale, improved, as did sleep, intradialytic cramps, appetite and energy level. The overnight technique did not appear to induce fatigue or increased intrusion into daily life. Finally, at the 2008 annual meeting of the American Society of Nephrology, OK and colleagues from Turkey described the results of 224 patients switched from conventional to 8 h INHD (10). When compared prospectively with a matched cohort of patients on conventional 4-h hemodialysis 3 d/wk, the INHD patients had 25% as many hospitalizations, less intradialytic hypotension, lower phosphorus, reduced arterial stiffness and improved cognitive function. Remarkably, the authors reported INHD patients had a 78% reduction in mortality. INHD has been growing rapidly in the United States: the two largest dialysis providers reported treating more than 1600 patients with INHD in March 2009. Dialysis providers may find INHD a particu-
larly attractive way to provide more intensive dialysis — dialysis centers are usually closed at night, so the marginal cost to establish an INHD program is less than for opening conventional daytime dialysis. Bujea et al. describe several barriers to INHD, including nurse recruitment, nocturnal physician visits and the need to accommodate comfortable sleep for patients (9).

**Daily, Short Duration Hemodialysis**

Many case reports and small series of patients treated with daily, short duration hemodialysis have been published. Suri and colleagues published a systematic review of these reports in 2006 (11). After screening more than 800 citations, 233 full text articles were reviewed in detail. Only 25 of them met these inclusion criteria: five or more adult patients, follow-up of at least 3 mo, dialysis prescription of 1.5 to 3 h, 5 to 7 d/wk and published after 1989. A systematic review of these 25 publications showed consistently improved BP control and reduced left ventricular hypertrophy. However, the effects of daily hemodialysis on quality of life, anemia, phosphorus control and nutritional status were inconsistent. In 2008, Kjellstrand and colleagues reported their long-term experience with 415 daily hemodialysis patients (12), 265 treated at home and 150 treated in-center. Patients were on daily dialysis for 2.4 ± 2.6 yr, for a total of 1006 patient-years. Forty-two percent of patients were alive after 10 yr of daily hemodialysis and the death rate was 84 deaths of 1000 patient-years. When this survival rate was compared with survival as reported in the USRDS 2005 Annual Data report, and patients were matched for age, diagnosis and place of dialysis, the relative rate of mortality of daily hemodialysis patients was 0.35 to 0.83 of that of the matched USRDS cohort. The standardized mortality ratio was 0.34, a highly significant reduction in mortality. Life expectancy for the daily dialysis patients was 9 to 15 yr longer than those of the matched USRDS hemodialysis cohort, and was similar to deceased donor kidney transplant recipients.

**Nocturnal Home Hemodialysis**

Nocturnal home hemodialysis (NHHD), performed four to six times a week, offers the most marked enhancement of small and large molecule clearance. It also allows for more gradual ultrafiltration, enabling maintenance of “dry weight” with low hourly ultrafiltration, favoring better survival (7). Walsh et al. reviewed the published observational studies of NHHD (13). Four patient cohorts from London and Toronto, Ontario, Lynchburg Virginia and Rochester Minnesota, were examined. Study sample sizes ranged from 5 – 63 NHHD patients followed for 6 wk to 3.4 yr. Improved BP control, anemia and health-related quality of life were consistent findings. There is evidence that NHHD upregulates genes responsible for hematopoetic progenitor cells, increasing growth and production of red blood cells (14). Sixteen patients treated with NHHD showed increased hemoglobin from 11.3 ± 0.3 to 12.5 ± 0.4 Gm/dl with no change in erythropoetin or iron dose. This group of investigators from Toronto has also shown evidence from observational studies that NHHD reduces cardiovascular related hospitalizations (15), improves the baroreflex effective-ness index and baroreflex sensitivity (16), improves sleep apnea by increasing pharyngeal size (17) and improves cognition (18). In 2007, Culleton and colleagues (19) published results of a randomized controlled trial (RCT) comparing NHHD performed five to six nights per week for a minimum of 6 h per night to conventional thrice weekly hemodialysis. Left ventricular mass decreased significantly in the NHHD group, while it remained unchanged in the conventional dialysis patients. In addition, BP fell with the use of fewer antihypertensives, and phosphorus levels and parathyroid hormone levels fell in the NHHD group. While the primary quality of life outcome was not different than control, NHHD was associated with improvements in selected kidney-specific quality-of-life domains (20). Although this study was not powered to examine survival or hospitalization rates, this first published RCT of NHHD did show improved cardiac and quality-of-life measures, which have been shown to correlate with survival in dialysis patients (21-23). This is an exciting finding, in light of previous RCTs examining higher dose dialysis for end-stage renal disease (HEMO (3) and ADEMEX (24) trials), and for acute kidney injury (25) that failed to show a beneficial effect. If NHHD really does offer improved outcomes, how likely is it that patients will choose this dialysis modality? Cafazzo et al. reported several patient-perceived barriers to NHHD (26). Fifty-six nocturnal hemodialysis patients and 153 conventional hemodialysis patients completed surveys concerning their perceptions of their disease condition and overall health, benefit, barriers and self-efficacy of NHHD and factors affecting decision making. NHHD patients were healthier and had better physical quality-of-life scores. The barriers to NHHD identified were fear of self-cannulation, lack of confidence in conducting NHHD and fear of a catastrophic event. The burden this therapy placed on family members was also a perceived barrier.

**The Frequent Hemodialysis Network (FHN)**

Given the promising results of many observational studies and a single RCT of more frequent hemodialysis, the National Institute of Digestive Diseases and the Kidney and the Center for Medicare and Medicaid Services have funded the FHN trials. These two parallel RCTs, one examining short in-center daily dialysis versus conventional thrice weekly dialysis, and the other studying NHHD versus thrice weekly conventional HD at home, are currently underway (27,28). We have recruited and randomized 245 subjects in the daily in-center trial, and 87 subjects in the NHHD trial. Subjects will be studied in an intention-to-treat analysis that compares outcomes after 1 yr. These studies are not sufficiently powered to examine mortality or hospitalization rates, so surrogate outcomes will be examined that we believe will correlate with mortality and with quality of life, two outcomes of importance to dialysis patients. Co-primary outcomes are: 1) a composite of 1-yr mortality and change in left ventricular mass as measured by cardiac cine-MRI, and 2) a composite of 1-yr mortality and change in RAND Physical Health Component Score from the SF-36 quality-of-life assessment tool. Secondary outcomes include assessments of depression, cognitive function, nutrition and inflammation, mineral metabolism, survival, hospitalization, hypertension
and anemia. The study period will end in the first part of 2010, and we expect to report results in 2010 and 2011.

Cost-Effectiveness of Frequent Hemodialysis

Given the high cost of treating dialysis patients, an important question is what effect more intensive therapies will have on the overall cost. Will more frequent treatments bring down the cost of individual dialysis sessions? If more intensive dialysis results in improved survival and reduced hospitalizations, what effect will these have on costs? Lee and colleagues examined these questions for in-center daily hemodialysis using a Monte Carlo simulation model (29). Inputs into the model included various frequencies and duration of hemodialysis (three to six times per week, 2 to 4.5 h per session), several outcomes (costs, life expectancy and quality-adjusted life years) and assumptions for the potential effects of frequent dialysis on outcomes (for example, one input was a 32% reduction in mortality with six times per wk treatments). They found that the incremental cost-effectiveness ratio will be at least $75,000 per life year gained, and that none of the strategies using six-times-per-week hemodialysis achieved a cost-effectiveness ratio of less than $125,000 per life-year gained. Since we live in a world where payers often seek “cost-neutral” treatment solutions, they asked the question, under what circumstances might costs “break even” — i.e., what improvements in outcomes would be needed to result in no net increase in cost? Their model suggested that costs could break even if the per-session dialysis costs were reduced between 32% and 43%. Might reduced hospitalizations result in costs breaking even? Their model showed that for four-times-a-week dialysis, hospitalization rates would have to be reduced to 46% of current rates for cost to break even. For five-times-a-week treatments, hospitalizations would need to be completely eliminated to break even, and six times-a-week treatments will never break even. They conclude that more frequent in-center hemodialysis strategies would likely increase ESRD program costs considerably. They suggest that transition to home-based therapies will be required to derive any benefit that might be present without incurring excessive costs.

The International Quotidian Dialysis Registry

Well-designed studies examining mortality and hospitalization for patients with heart disease are plentiful, but are remarkably few in nephrology (30). This may in part be the result of the many patients with heart disease, compared with the relatively few with advanced kidney disease. ESRD patients may be particularly reluctant to enroll in RCT because of their multisystem disease and the toll that dialysis takes on their lives (31). For whatever reason this difference exists, the low numbers of patients willing to enter RCTs make assessments of hard endpoints such as mortality and hospitalization rates difficult to assess: previous studies are underpowered to examine these outcomes. Perhaps the best chance to assess them will come with the International Quotidian Dialysis Registry (32). This registry, established in 2002, has enrolled more than 2700 patients, all on alternate hemodialysis schedules. Patients are accepted into the registry if they receive more than 5 h per threice-weekly treatment session or ≥5 treatment sessions per week. Treatments may be daytime or nightly, in-center or at home. The order of magnitude higher number of enrolled subjects studied prospectively should allow analysis of mortality and other clinical endpoints for these alternate dialysis regimens.

Conclusions

• More intensive dialysis is needed to improve patient outcomes.
• NHHD reduces left ventricular hypertrophy.
• Observational trials suggest better anemia care, phosphorus control, fluid and BP management, baroreflex sensitivity, cognition and less sleep apnea with intensive hemodialysis.
• Retrospective analysis shows improved survival with intensive dialysis.
• Cohort studies show reduced cardiovascular-related hospitalizations with NHHD.
• Frequent in-center hemodialysis (four to six treatments/wk) is more costly — unless per-treatment costs fall.
• Frequent home hemodialysis (four to six times a week) and NHHD are promising, but are currently utilized by few patients.
• INHD is the fastest growing type of more intensive hemodialysis, with more efficient use of facility space, improving financial viability.
• The FHN, two RCT of NHHD and daily in-center hemodialysis are in progress.
• The International Quotidian Dialysis registry may give us meaningful information on the effect of intensive hemodialysis on mortality and hospitalization.

Disclosures

None.

References

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