Ten Years Experience of In-Center Thrice Weekly Long Overnight Hemodialysis

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Background and objectives: Published studies suggest that longer hemodialysis (HD) sessions are associated with improved morbidity and mortality, but few centers offer long sessions. The Western Infirmary renal unit has offered long overnight hemodialysis (LOH) (6 to 7 h) thrice weekly since 1998. The aim of this study was to describe patients who chose LOH and compare outcomes with patients on conventional hours (4 to 5 h) HD.

Design, settings, participants, & measurements: Patients who ever had LOH for three or more consecutive sessions were identified (n = 146). Indices of urea reduction ratio (URR), anemia, hyperphosphatemia, and predialysis BP (BP) control in a subgroup of all patients on LOH for at least 1 yr since 2004 were compared with age, sex, and diabetes-matched controls undergoing conventional duration HD.

Results: The mean age at the time of starting LOH was 51.8 yr and 74.7% started with a functioning arteriovenous fistula. Median duration of continuous LOH was 1.6 yr. Of those no longer on LOH, only 33.3% reverted to conventional hours HD (mean duration LOH 2.2 yr). When comparing LOH and conventional HD cohorts, there was increased URR and mean hemoglobin with a trend toward lower mean erythropoietin index. There was a trend toward fewer phosphate binder tablets but no difference in mean serum phosphate, BP, or number of prescribed antihypertensive medicines.

Conclusions: LOH is a well tolerated hemodialysis option, associated with improved URR and better control of anemia.

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There is no consensus on the optimal duration or frequency of hemodialysis sessions for patients with established renal failure, but constraints on time and resources mean that 3 to 5 hr, three times a week hemodialysis is routine practice for most hemodialysis units.

Most of the evidence relating to dialysis session duration comes from small observational, single-center studies, but one randomized control trial has been performed in the United States (1). Several of these centers have reported data suggesting more frequent or longer hemodialysis sessions may be associated with improvements in all or some of the following: small solute clearance, BP control, left ventricular hypertrophy, anemia, hyperphosphatemia, nutritional parameters, and mortality (2–9).

The Western Infirmary renal unit has offered long overnight hemodialysis (LOH) since 1998. This consists of 6 to 7 h sessions three times per week at the main unit and one of our satellite units. The unit decided to provide thrice weekly in-center LOH in the belief that improved solute clearance and more prolonged ultrafiltration might be associated with improved outcomes and that the option of overnight hemodialysis might be socially attractive to some patients, as well as to increase dialysis capacity. We place few restrictions on the type of patients who can receive LOH. Patients are offered LOH if they do not need a two-person ambulance to take them to and from their dialysis sessions and are prepared to travel home from dialysis sessions at 2 to 4 a.m.

The aim of this study was to describe all of the patients who chose LOH over the 10-yr period. In a subset of these patients, a case-controlled analysis was also performed of the impact of LOH on small solute clearance, hyperphosphatemia, anemia, and BP compared with age, sex, and diabetes-matched controls undergoing conventional duration hemodialysis (HD). The study hoped to demonstrate that LOH was a suitable modality for the majority of dialysis patients and would be associated with clinically meaningful benefits.

Materials and Methods

Subjects

All patients who had ever had LOH for more than three consecutive sessions were identified from the electronic patient record (EPR) along with data concerning age, sex, primary renal diagnosis, and duration of renal replacement therapy at the time of starting LOH. The subsequent duration of LOH was calculated and the reason for stopping identified.

Case-Controlled Study

All patients who had been on LOH continuously for at least a year after January 1, 2005, were identified. Each patient was matched with a

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patient from the pool of those who had been on conventional hours day-time HD for at least 12 mo continuously after January 1, 2005. Controls were matched for age (within 5 yr), sex, and presence or absence of diabetes. The reason for selecting January 1, 2005, is that patient medication and dose was recorded prospectively on the EPR after January 1, 2005.

Hemodialysis was performed using biocompatible low flux membranes with blood flows of 400ml/min where possible, dialysate flow of 500–700ml/min, and standard bicarbonate dialysate. Monthly measures of urea reduction ratio (URR), hemoglobin (Hb), serum ferritin, erythropoietin stimulating agent (ESA) dose, ESA index (dose/kg/g/Hb), intravenous iron saccharate dose/wk, predialysis serum phosphate, predialysis systolic BP (SBP), number of prescribed phosphate binder tablets, and number of prescribed antihypertensive agents were averaged over three consecutive months after January 1, 2005. ESA dose was expressed as international units (iu) of erythropoietin; the weekly dose in μg in the patients taking darbapoietin (n = 32) was multiplied by 200 to give an erythropoietin equivalent. Antihypertensive agents were compared both as number of different agents prescribed and as number of doses of the standard minimum daily dose of each agent per day. In both patient groups, treatment was adjusted monthly to achieve national standards of URR (>65%) (10), Hb (10.5 to 12.5 g/L), serum ferritin (>100 μg/L), and predialysis serum phosphate (1.1 to 1.8 mmol/L) (11).

Statistical Analyses

For the case-controlled study, variables were compared by *t* test of mean or chi-square test where appropriate and $P < 0.05$ was regarded as statistically significant.

Results

Patients

Since 1998, 146 patients (123 in the main unit and 23 in the satellite unit) have chosen LOH. This represents 11.3% of the total number of patients who have been on dialysis for established renal failure in our center during the same period. Mean age at time of starting LOH was 51.8 yr (SD 14.6). Twenty-five patients were on LOH while >70 yr and five were on LOH while >80 yr. 110 (75.3%) patients who chose LOH were male. Median duration of renal replacement therapy before starting LOH was 1.4 yr (range 0.0 to 28.3). Primary renal diagnosis was: primary glomerulopathy (31.5%), cause unknown (17.1%), diabetic nephropathy (14.4%), renovascular disease (14.3%), chronic pyelonephritis (10.3%), and others (12.4%).

One hundred nine patients (74.7%) started LOH with a functioning arteriovenous fistula, with the remainder starting with a tunnelled central venous catheter.

Duration of LOH and Reasons for Stopping

Median duration of LOH was 1.6 yr (range 0.03 to 9.71) and 113 of patients continued LOH for at least 6 mo. Twenty-nine patients remained on LOH at January 1, 2008. Reasons for stopping LOH were: transplant (42.7%), change back to conventional hours (33.3%), death (15.4%), transfer to another unit (7.7%), and change to peritoneal dialysis (0.9%).

Of those patients converting back to conventional duration HD, the mean duration of LOH before modality fatigue was 2.2 yr. There were no significant differences in age, sex, diabetes, duration of RRT before LOH, or likelihood of subsequent transplant in patients who returned to conventional HD within 6 mo and those continuing LOH for at least 6 mo (Table 1).

Case-Control Study

Fifty-three patients who had been on LOH continuously for at least 1 yr after January 1, 2005, were matched with 53 controls as described above. In patients where it was not possible to find a control matched for the presence of diabetes (n = 2), a patient without diabetes was selected. Baseline demographic data are shown in Table 2. As expected, age, sex, and diabetes incidence were comparable, and duration of renal replacement therapy (RRT) at the time of data collection was also similar. The proportion of patients in each group who subsequently received a kidney transplant was similar, providing further evidence that the groups were comparable.

The clinical data are summarized in Table 3. As expected, the URR was significantly higher in the LOH patients (77.1% *versus* 71.6%; $P < 0.0001$). The mean Hb was significantly higher in the LOH patients (121.9 *versus* 114.9 g/L; $P = 0.01$) with a trend toward a lower mean ESA index (0.77 v 1.2 iu/wk/kg/gHb; $P = 0.06$). There was no difference in mean serum phosphate but there was a suggestion that this was achieved with fewer prescribed phosphate binder tablets in the LOH group (4.8

Table 1. Comparison between patients who remained on long overnight hemodialysis (LOH) for at least 6 mo and those who returned to conventional HD within 6 mo

	Returned to Conventional HD within 6 mo [$n = 21$]	Remained on LOH for at least 6 mo [$n = 113$]	P
Age (yrs) [sd]	50.6 [15.2]	52.8 [14.3]	0.52
Male (%)	15.0 (71.4)	86.0 (76.1)	0.65
Diabetes (%)	2.0 (0.1)	5.0 (4.4)	0.34
Subsequently received a kidney transplant (%)	7.0 (33.3)	43.0 (38.1)	0.68
Duration RRT before LOH			
<2 yr (%)	15.0 (71.4)	59.0 (52.2)	0.11
2–5 yr (%)	2.0 (9.5)	25.0 (22.1)	0.19
>5 yr (%)	4.0 (19.0)	29.0 (25.7)	0.52

Age is quoted in this table as a mean.

Table 2. Baseline demographic data for the case controlled comparison of patients on LOH for at least 1 yr after 2004 and age, sex, and diabetes-matched control patients on conventional hours HD

	LOH HD (n = 53)	Conventional HD (n = 53)	P
Mean age (yrs) [sd]	50.3 [15.7]	52.0 [15.5]	0.58
Male (%)	75.5	73.6	0.82
Diabetes (%)	17.0	13.2	0.61
Mean target weight (kg) [sd]	84.4 [20.7]	72.2 [18.5]	0.002
Subsequently received a kidney transplant (%)	28.3	32.1	0.67
Duration RRT			
1–2 yr (%)	28.3	24.5	0.66
2–5 yr (%)	26.4	26.4	1.00
>5 yr (%)	45.2	49.1	0.70

Table 3. Comparison of hemodialysis-related data averaged over three consecutive months

	LOH HD (n = 53)	Conventional HD (n = 53)	P
URR (%)	77.1 [7.3]	71.6 [8.2]	<0.01
Haemoglobin (g/L)	121.9 [12.8]	114.9 [1.6]	0.01
Ferritin (μg/L)	491.8 [307.8]	455.2 [334.8]	0.56
ESA dose (iu/wk)[a]	8100.6 [7742.3]	8289.3 [7532.6]	0.90
ESA dose (iu/wk/kg)	90.8 [77.4]	125.71 [135.12]	0.11
ESA index (iu/wk/kg/gHb)	0.77 [0.68]	1.2 [1.4]	0.06
IV iron dose (mg/wk)	48.6 [51.7]	55.7 [48.7]	0.47
IV iron dose (mg/wk/kg)	0.57 [0.64]	0.79 [0.66]	0.09
Serum phosphate (mmol/L)	1.75 [0.46]	1.78 [0.49]	0.74
Prescribed phosphate binders (%)	86.8	92.5	0.34
Number of phosphate binder tabs per day	4.8 [2.6]	5.9 [3.6]	0.08
Pre-dialysis systolic BP (mmHg)	134.9 [28.7]	139.9 [25.2]	0.34
Number of antihypertensive medications prescribed/day	0.87 [1.11]	0.92 [1.06]	0.79
No. of antihypertensive agent standard minimum daily doses/day	4.5 [7.6]	3.6 [5.5]	0.52

All data presented as a mean [sd].
[a]ESA dose, erythropoietin equivalent. For the 32 patients on darbepoietin, the weekly dose in μg was multiplied by 200 to give the erythropoietin equivalent.

versus 5.9 tablets per day; $P = 0.08$). There was no significant difference in predialysis systolic BP or number of prescribed antihypertensive medicines.

Discussion

Thrice weekly hemodialysis for 3 to 5 h has become the standard dialysis prescription in most centers worldwide out of logistical convenience rather than scientific titration. Many authors have discussed the inadequacy of this regimen, but finding alternative solutions that are tolerated by patients and are economically viable, given the massive increase in demand for long-term hemodialysis, has proved difficult. Options such as short, daily dialysis or long, nocturnal dialysis at home five to seven times per week are physiologically attractive but require a dedicated program and highly selected patients. Longer dialysis is potentially beneficial for several reasons, including reduced hemodynamic instability related to lower ultrafiltration rates, increased small solute removal, and improved removal of middle molecules. All of these factors have potentially beneficial effects on the massively increased risk of cardiovascular death associated with established renal failure (12). In-center LOH, as described in our study, is more easily available to patients at high risk of cardiovascular death than short, daily HD or nocturnal HD five to seven times per week, both of which are restricted mainly to patients suitable for home therapy.

The prime motivation for providing LOH in our center was the belief that longer dialysis might improve outcome and that the option of overnight hemodialysis might be socially attractive to some patients. It also allowed an increase in dialysis capacity without an increase in real estate, although this was a secondary consideration. We were keen not to restrict it to young, fit patients, although overnight dialysis can be a convenient option for patients who wish to continue working during

the day. Thus, all patients who do not need a special ambulance for transport are offered LOH as an option. Sometimes we suggest LOH as a good option for patients who have large interdialytic fluid gains, inadequate URR, uraemic symptoms on conventional duration dialysis, or for patients who are likely to be on dialysis for a long period due to a low probability of transplantation (*e.g.,* highly sensitized patients). Our data show that just over 10% patients have chosen LOH in the last 10 yr. Our lack of clinical exclusion criteria for LOH is reflected in the diverse range of primary renal diagnosis, diverse age of our cohort (with several patients on LOH in their ninth decade), the fact that almost 25% of patients started LOH with a tunnelled central venous catheter (which is similar to the proportion with a tunnelled central venous catheter on conventional hours HD), and the proportion of patients who subsequently received a transplant being similar to the conventional hours cohort. The body weight was higher in patients receiving LOH, however. It is difficult to know if this reflects deliberate selection of larger patients for LOH to try to improve small solute clearance, or better nutritional state. Our results show that LOH is well tolerated as evidenced by the fact that the most common reason for discontinuing LOH was to receive a kidney transplant and that the patients' mean duration of LOH before conversion to conventional hours HD was 2.2 yr. Only about a third of patients left LOH to go back on conventional HD, and this was usually patient choice rather than a change in medical condition. No serious adverse events directly attributable to LOH were reported in these patients. Also, we found no factors that predicted which patients would switch to conventional hours HD within 6 mo of starting LOH.

Our subjective impression is that many patients who change from conventional HD look and feel better after only a few weeks of LOH. This is consistent with reports from other centers that offer longer dialysis (13), but is difficult to measure as it is difficult to remove observer bias, selection bias, and survival bias. When patients were matched for age, sex, and presence of diabetes in an attempt to minimize selection bias, we found significantly improved URR and anemia control in patients on LOH compared with controls.

Only one randomized controlled trial has been undertaken to determine the effects of increased dialysis session duration. This study conducted in the United States was published in 1981 and enrolled 151 patients (National Cooperative Dialysis study, or NCDS). Patients were randomized into four groups in this 2 × 2 factorial design: low target time averaged urea concentration (BUN – 50 mg/dl), high BUN (100 mg/dl), and short (2.5 to 3.5 h) or long (4.5 to 5.5 h) thrice-weekly dialysis sessions. Their findings showed no significant difference in mortality between the four groups. However, the study was stopped early (after only 22 mo) due to the significantly greater withdrawal due to hospitalization or death in the high-BUN groups. Dialysis treatment time, however, had no significant effects on hospitalization (10). This study and the adoption of a urea-reduction based model of dialysis had a significant influence especially in America, where it became popular to aim for a target dialysis dose (*i.e.*, Kt/v or URR) rather than session length (14).

Following this, a number of other observational and case-controlled studies of long dialysis were published. The best known of these is from the Tassin Unit in France (n = 876), where they have more than 20 yr of experience of dialyzing patients for 8 h three times a week. They reported dramatically improved survival rates compared with rates published from other centers around the world, including 99% 5 yr survival for the age-group 45 to 54 yr old. Other benefits included excellent control of BP without the need for antihypertensive medication, reduced ESA dose, and better phosphate control (2,15).

A group in Germany published a non-randomized study comparing nocturnal thrice weekly dialysis of 7.5 to 8 h (n = 11) with standard HD (n = 13) and daily short HD (6 × 2.5 to 3 h) (n = 6) (9). They found a significant reduction in left ventricular mass index, fractional shortening, ventricular ectopic beats, number of antihypertensive tablets, and mean predialysis systolic BP in both the daily and nocturnal dialysis groups. However, their primary end point of 24 h BP control was not significantly different between the three groups. It is worth noting, however, that the overnight dialysis was chosen by significantly younger and healthier individuals in this study.

Two recent, large multi-center observational studies have attempted to address the question of dialysis-session duration. Analysis of the DOPPS (Dialysis Outcomes and Practice Patterns) study data suggests that every extra 30 min spent on dialysis was associated with a 7% lower relative risk of death (16). An analysis of data from the Australian and New Zealand dialysis registry data suggested that Kt/V of 1.30 to 1.39 and a session length of 4.5 to 4.9 h were associated with the lowest adjusted mortality risk, but the analysis was inadequately powered to detect any survival advantage for patients dialyzing for more than 5 h per session (17). One of the difficulties in interpreting the conclusions of these multi-center observational studies is that it is hard to control for other features of the dialysis session, such as small solute clearance, blood flow rates, dialysis membrane characteristics, ultrafiltration practices, and dialysate composition. Single-center studies such as ours have the advantage that most of these dialysis-related practices are relatively uniform.

Our observation, that BP control was no better in the LOH cohort than the conventional group, contrasts with data from the Tassin study (18). The Tassin group attributed its good BP control to better control of extracellular fluid overload. The West of Scotland diet has a notoriously high salt content, and it is possible that salt intake negates the potential beneficial effects of LOH on BP, despite the dietary advice the patients receive. We had no prospectively collected diet diaries or timed urine collection to test this hypothesis. Furthermore our retrospective study could not assess the change in BP in individual patients as they move from conventional dialysis to LOH.

The lack of difference in phosphate control was a surprise. It would be interesting to compare dietary phosphate intake in the two groups to determine if the apparent lack of a benefit of LOH on phosphate control was explained by increased dietary phosphate intake, since our subjective impression is that the patients on LOH do not need to restrict dietary intake of phosphate as much as those on conventional HD. This would

tally with our observation of apparently lower binder ingestion in the LOH group. Given the consistent improvement in all parameters we were able to study, we suspect a type 2 error and that the number of patients studied was insufficient to detect a significant difference in phosphate or BP control, despite being larger than previous similar single-center reports.

The retrospective nature of the selection of controls is a potential limitation. We controlled for age, sex, and diabetes, but this does not exclude the possibility that significant differences in other variables introduced selection bias in the analyses we performed. Despite our attempt to compare similar patients, it is still likely that patients choosing LOH are either fitter (because they choose LOH because they are more active during the day) or are better nourished (and encouraged to select LOH to enable them to achieve adequate URR). These factors are likely to be associated with improved outcomes, and the latter possibility is supported by the significantly higher weight in the LOH patients. These limitations are also a problem with the previously published comparative studies described. An adequately controlled, randomized-controlled trial is highly desirable to determine the comparative merits of longer and more frequent HD regimens, but few patients are likely to be willing to be randomly allocated a regimen, and such studies will be expensive to conduct. Thus, observational data, preferably collected prospectively, from large programs of non-conventional HD regimens are likely to remain the best available source of comparative data to aid clinical decision making about the optimal duration of HD sessions. It would be interesting to compare other factors such as hospitalizations, access patency, intradialytic hypotension episodes, and quality of life, and these are the subject of on-going prospective studies.

Conclusion

Our experience of LOH in the last 10 yr shows that it is a practical way for dialysis units to offer longer dialysis that is well tolerated by a substantial proportion of the HD population and does not need to be restricted to the fittest patients. There were significant improvements in URR and anemia but, in contrast to previous reports, no significant differences in hyperphosphatemia or hypertension. The potential impact on morbidity and mortality is the subject of on-going research.

Disclosures

None.

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