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Nocturnal versus conventional haemodialysis: some current issues

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Introduction

The burden of kidney disease continues to grow in the United States, and more patients are faced with the need for dialysis [1]. While haemodialysis is a life-saving form of renal replacement therapy, the long-term outlook for patients on the conventional dialysis regimen of 4 h per session three times per week is grim: mortality four times higher than the general population for dialysis patients under 30 and six times higher than the general population for dialysis patients over 65 [2]. The number of patients on home haemodialysis—both conventional haemodialysis (CHD) and nocturnal haemodialysis (NHD)—represents a small fraction of the end-stage renal disease population (ESRD) in the USA and Canada, ~1500 in 2003, ~0.4% of all dialysis patients in the USA [3]. A survey of dialysis machine manufacturers in 2007 estimated that ~1% of ESRD patients in the USA were doing home dialysis [4].

Home haemodialysis enjoyed early success in the USA with ~40% of all dialysis patients treated at home at one point [5]. Scribner and colleagues carried out the first nocturnal dialysis in Seattle in the 1960s, using a pumpless plate dialyser [6]. De Palma and colleagues undertook the earliest daily dialysis with a reusable coil dialyser and blood pump [7]. But their early experiment in daily and nocturnal dialysis failed because ‘economic considerations—not quality machinery and ergonomics—came first’ [4]. Others attributed the decline in home haemodialysis and NHD to the advent of continuous ambulatory peritoneal dialysis in the 1970s, improvements in cadaveric transplant survival with the advent of cyclosporine in the 1980s and increased use of living donor kidneys in the 1990s [3].

The USA initially funded home haemodialysis programmes to counter growing costs of in-centre dialysis, but home dialysis fell further out of popularity with passage of amendments to the Social Security act on dialysis payment in 1972 since in-centre dialysis was able to deliver minimum adequacy with three sessions per week [8].

Home NHD is now a little used modality. According to data from the US Renal Data System, only 0.2% of the incident ESRD patients in 2004 started on home haemodialysis of any sort. Of the 472 099 prevalent patients, only 0.4% were on home haemodialysis [9]. In 2005, 428 of 104 018 incident dialysis patients started on home haemodialysis, and 2105 of 340 057 prevalent dialysis patients were on home haemodialysis. In the USA, home haemodialysis patients are less likely to be African American and Hispanic than in-centre dialysis patients [10].

A survey of all known daily dialysis programmes in the USA found 13 centres in North America performing daily NHD as of January 2001, caring for 115 patients [11]. The International Quotidian Dialysis Registry in Ontario recorded 229 patients in 2007, up from 199 in 2006 [12].

Yet data have accumulated showing advantages to more frequent daily or nocturnal dialysis. Based on his experiences observing patients in the intensive care unit [13], Robert Uldall in Toronto initiated a 2-year pilot study with a grant from the government of Ontario to evaluate what he called simplified nocturnal home haemodialysis [14]. He reasoned that frequent long dialysis sessions produced fewer symptoms than short intermittent treatments; at-home dialysis was less expensive than in-centre dialysis; nocturnal dialysis was less disruptive than daytime dialysis.

The programme started enrolling the first of 36 patients in 1994. The 30 patients enrolled at 5 years showed improvements in blood pressure, mineral metabolism and cognitive functioning. There was no difference in haemoglobin levels or erythropoietin use [15]. By 2003, the group had trained 90 patients and was dialysing 48 patients nightly and 5 every other night for a total experience of 230 patient-years [16].
A growing body of literature—much from the Canadian experience, as well as from Australia—suggests that NHD may offer improved outcomes on a number of surrogate markers for mortality. This review will examine that data and efforts to see whether those improvements mean increased patient survival.

**Blood pressure and left ventricular hypertrophy**

The exact relationship of blood pressure with mortality in ESRD remains unclear, with some arguing that ESRD patients should be treated differently in terms of blood pressure targets [17]. But most experts agree that blood pressure control remains an important endpoint in the ESRD population, even if data are mostly observational, given the association between blood pressure and cardiovascular outcomes. Early observational studies of blood pressure control in NHD found an association with other known surrogate markers for mortality in the ESRD population such as left ventricular hypertrophy, which is associated with sudden cardiac death [18], fatal and nonfatal myocardial events [19] and cardiovascular disease [20].

An early observational study compared 28 patients converted to NHD from CHD with 13 patients on self-care conventional home haemodialysis over 3 years with similar baseline blood pressures and anti-hypertensive use. The nocturnal group showed significant drops in systolic, diastolic and mean arterial pressures from baseline as well as a reduction in left ventricular mass index (LVMI) as measured by 2-D echocardiogram. In addition, those in the NHD group were able to reduce their BP medicine requirements, whereas those in the CHD had no change. Researchers found no correlation between the decrease in LVMI and reduction in blood pressure or extracellular fluid (ECF) volume in the NHD group [21].

The London (Ont.) Daily/Nocturnal Haemodialysis Study [22], a nonrandomized prospective study comparing quotidian dialysis with conventional dialysis, found a significant drop in pre-dialysis mean arterial blood pressure on NHD. Importantly, given similar intra-dialytic weight gains and similar ECF volumes as measured by electrical bioimpedence, this decrement in blood pressure was thought to be related to volume [23].

How NHD might improve blood pressure independent of volume remains uncertain, with some investigators suggesting that nocturnal dialysis lowers levels of serum norepinephrine [24]. NHD patients also have an improved heart-rate response to pulsatile blood pressure, suggesting improved baroreceptor response and arterial compliance [25,26]. Some suggest that NHD may play a role in improved blood pressure and cardiovascular outcomes through improvements in sleep apnea. The mechanism is not entirely clear [27]. It is known that hypoxia improves with correction of sleep apnea [28], and NHD may play a role through improvements in vagal and sympathetically mediated heart rate [29]. There may also be an additional survival benefit from the slower ultrafiltration rate over a longer period of time [30].

The first randomized controlled study recently compared the effects of NHD with CHD on change in left ventricular mass as measured by cardiac MRI, the primary outcome. Followed over 6 months, the NHD group showed a significant decrease in LV mass [31]. Sixteen out of 26 NHD patients discontinued blood pressure medications compared with 3 out 25 in the CHD group, again a significant difference. Despite this reduction in anti-hypertensive medication, 6-month systolic blood pressure decreased by 7 mmHg in patients randomized to NHD and increased by 4 mmHg in those randomized to CHD (mean difference 11 mmHg; 95% CI, −2 to 24 mmHg). When adjusted for baseline systolic blood pressure, this difference increased to 14 mmHg (95% CI, 3–26 mmHg; P = 0.01). Notably, ECF volume was not included in this study.

Observational data suggest that NHD provides better blood pressure control than conventional dialysis and leads to improvements in left ventricular hypertrophy. This may be due to multiple factors, independent of volume control, and suggest that the prolonged and slow flows of nocturnal treatments may lead to improved haemodynamic physiology. But other researchers have shown the role of removing extracellular volume in reduction of blood pressure and resolution of LVH in short daily treatments and extended standard dialysis, and this may be the case in nocturnal dialysis as well [32–34].

Observational data suggest that NHD may improve anaemia without an increase in erythropoietin use, in part through effects on haematopoietic progenitor cell growth [35]. A meta-analysis of data on LVMI and anaemia suggests that LVMI in patients with severe anaemia improved with correction of anaemia to conventional targets on erythropoietin [36]. And while data are awaited on a composite outcome including mortality, a small cohort study found a significant reduction in hospital admissions for cardiovascular causes in a group on nocturnal dialysis compared with a group on conventional dialysis [37].

**Calcium and phosphorus**

A growing body of evidence suggests that improved mortality in dialysis patients relates to mineral metabolism parameters. Observational studies and the sole randomized controlled trial have shown improvements in phosphate handling on NHD compared to CHD.

An observational study suggested that NHD reduced serum phosphate levels, allowing the cessation of phosphate binders in many patients. Some even require phosphate supplementation [38]. In the only randomized controlled trial, no significant difference in serum calcium levels between patients on NHD and CHD was found. However, those on NHD had significantly lower serum phosphorus levels (95% CI −2.5 to −0.5, P < 0.01 and >0.001). Calcium–phosphorus product was also significantly lower in the NHD group by 13.6 mg²/dL² than in the CHD group (95% CI −22.3 to −4.3, P ≤ 0.01 and >0.001). Elemental calcium use in the NHD group dropped to 750 mg/day compared to no change in the CHD (P < 0.001). Overall, oral phosphate binders were eliminated in 19/26
patients in the NHD group and only 3/25 in the CHD group [31].

Most investigators have found that phosphate clearance is better on NHD than on conventional treatment. Some researchers suggest that this is due to the increased time on NHD compared to that on conventional treatment [39–41]. Other researchers, however, suggest that the frequency of daily treatments, rather than the cumulative time of weekly treatments, is most important in phosphate clearance [42]. In addition, the slow flow of nocturnal treatment might allow more efficient equilibration between the intracellular and extracellular compartments, and hence, a better overall clearance while on dialysis.

**Dialysis dose**

Data on whether NHD delivers more dialysis than CHD are few and depend on the criteria one uses to define ‘adequacy’. But with adequacy defined broadly as more than urea clearance, NHD appears to deliver a larger dose of dialysis as a result of the longer time, with potential benefits.

Proponents of NHD argue that it achieves greater weekly solute removal through the longer treatment time and increased number of treatments. The London Daily/Nocturnal study [43] showed that nocturnal and short daily dialysis delivered more dialysis on a weekly and standardized basis than conventional dialysis, particularly when using a measure of adequacy allowing comparison among different modalities [44]. The study showed, however, that NHD provides less clearance per unit time than CHD because of slower blood and dialysate flow rates.

The only randomized controlled trial on NHD did not address the issue of dialysis ‘adequacy’. A recent European discussion on dialysis dose and frequency argued that the concept of dialysis adequacy should not only include more than clearance calculations based on laboratory data but should also take into account the patient’s clinical state [45].

In addition to clearance of small molecules, which is the conventional method for assessing adequacy, clearance of the so-called ‘middle molecules’ is likely to be clinically important. Again, due to the length and frequency of NHD, clearance of middle molecules seems to be superior with nocturnal than with conventional dialysis [46].

Subgroup analysis from the HEMO study showed that mean pre-dialysis \(\beta_2m\) levels over time, but not dialysate \(\beta_2m\) clearance, were predictive of all-cause mortality, independent of chronicity of dialysis and residual renal function [47]. Thus, the longer time on NHD may improve clearance of middle molecules such as \(\beta_2m\) with potential benefits for mortality.

A mathematical model comparing urea, \(\beta_2m\) and creatinine clearance expected in the two frequent haemodialysis Network trials (details below) showed greater separation between the nocturnal six times weekly regimen and its control arm than between the daytime six times weekly regimen and its control arm. The model further showed greater separation between the arms of the FHN trials compared to separation between the arms of the HEMO study [48].

**Nutrition**

The effect of NHD on nutrition remains controversial. Some investigators have suggested that NHD may have an anti-inflammatory effect [49,50], and thus could potentially improve catabolism. Some have found an improved appetite, energy and body weight in patients on NHD [51]. Others, however, have found that NHD is associated with a worse metabolic profile, including a general anabolic state [15], reduced serum albumin levels and a decrease in relative body weight [52]. Some have argued for a nutritional advantage to short daily haemodialysis over longer intermittent treatments since patients feel better and eat more [53]. Others suggest that longer blood exposure to dialysis membranes may affect albumin synthesis [54]. Dutch investigators reported improved appetite, energy and body weight in a small cohort of patients on NHD.

A more definitive look at the effects of nocturnal dialysis will need to await the results of an ongoing randomized controlled study that will examine nutrition and inflammation as a secondary outcome in comparing conventional, short daily and nocturnal dialysis, with the main nutritional outcome pre-dialysis serum albumin [55].

**Quality of life**

Several small nonrandomized studies have found patients reporting improved quality of life on NHD. But the only randomized controlled trial to date found no improvement in quality of life in the NHD arm, except on kidney-specific questions [27], a finding they confirmed in a follow-up study [56]. Responses from patients on nocturnal dialysis and peritoneal dialysis to questions about quality of life, depression and intrusiveness of illness found no difference between the two modalities [57]. Younger patients have suggested that they would be more willing to switch to NHD while older patients cited fear of dialysing without supervision, fear of performing their own dialysis, fear of change and fear of social isolation [58].

**Cost**

The cost of NHD may prevent more widespread use. Several Canadian groups have shown that quotidian dialysis is more cost effective than conventional dialysis when looking at it from the standpoint of quality-adjusted life years [59,60].

Data from 13 daily dialysis programmes around the world [61] showed the annual direct costs of NHD at $57 700 versus $57 400 for CHD at home, $60 800 for SDHD in centre and $68 400 for CHD. But the researchers noted that centres would incur additional costs of 10–20% in implementing daily dialysis. They further argued that most of the additional cost savings would not accrue to the dialysis centre but to patients and Medicare in the USA. They concluded that dialysis centres are unlikely to put into effect a treatment that increases their costs without additional incentives. The nocturnal dialysis programme in Lynchburg, VA, USA, calculated its cost per patient during training at $5019.3 and
reimbursement at $3023.24. The average monthly cost after training was $1745.89 and reimbursement was $1526.46. It calculated its total loss per patient year as $2,633.16 [62].

The US Congress asked its accounting arm, the General Accounting Office, to report to the House on the costs of home haemodialysis treatment and patient training for both peritoneal and home haemodialysis, including recommendations for payment methods that measure the cost of providing those services and take into account the mix of patients [63].

Revisions to the US Medicare regulations on ESRD published in April 2008 stressed the need for services provided to patients on home dialysis be equal to those provided to patients receiving in-centre dialysis, but did not discuss financing per se. The new regulations, which were to go into effect in October 2008, require dialysis facilities to provide services that include ‘Purchasing, leasing, renting, delivering, installing, repairing and maintaining medically necessary home dialysis supplies and equipment (including supportive equipment) prescribed by the attending physician’ [64].

New US estimates suggest that the effect of more frequent, in-centre dialysis sessions on hospitalizations must be more robust than assumed for the treatments to be economically viable—unless costs drop 32% to 43% [65]. European commentators have argued that the extra cost does not result in an extra health benefit and that instead money should be invested in alternative non-in-centre types of dialysis [66].

Future

More data are needed from randomized controlled trials to show whether more frequent dialysis treatments such as NHD and SDHD can improve mortality. The frequent haemodialysis network randomized trial will compare two quotidian dialysis groups with conventional dialysis. In the first group, patients will be randomized to receive either six daily in-centre dialysis sessions of 1.5–2.75 h duration or three times weekly in-centre CHD. In the second group, patients will be randomized to either six nights per week of nocturnal dialysis for 6–8 h at home or three times weekly home dialysis for a minimum of 2.5 h and an equilibrated Kt/V = 1.1. The primary outcome will be a composite change at 12 months in L VMI as measured by MRI and mortality and quality of life as measured by the SF-36 Rand Physical Health Composite and mortality [67].

The daily trial, which was scheduled to be completed in July 2009, hopes to recruit 250 patients. The nocturnal trial, which is due to be completed in January 2010, hopes to recruit 150 patients. Both studies are still recruiting participants [68].

A ‘More Frequent Dialysis’ trial hopes to recruit 300 patients for a nonrandomized open-label cross-over study comparing three times weekly CHD with 5-days-per-week SDHD and NHD, 6-days-per-week SDHD and NHD and every-other-day SDHD and NHD [69].

The need for further randomized controlled trials is great. Trials to date have been small, nonrandomized and ‘quasi-experimental’ ones in which patients served as their own controls, leading to questions about the internal validity of these studies and whether they could be generalized [70]. Some have even questioned the ethics of whether Medicare should pay for short daily and long nocturnal dialysis without scientific analysis to demonstrate a benefit [71].

Proponents of quotidian dialysis have pushed for greater follow-up of patients on NHD and SDHD, and the International Quotidian Dialysis Registry has increased its number to 2123 patients in 2008. Moreover, the registry hopes to improve capture of data on daily and nocturnal dialysis in Europe, with collaborations underway with the UK Renal Registry and the French Renal Epidemiology and Information Network [72]. Indeed, the registry argues that its data will likely have a greater effect on governments and dialysis providers than the NIH studies by providing hard data on survival and morbidity as well as techniques and treatment failure [73]. Researchers in Canada have established the Canadian Slow Long Nightly Extended Dialysis Programmes (CAN SLEEP), a multicentre cohort aimed at collecting clinical data on NHD to improve the quality of nocturnal home haemodialysis Programmes [74].

Conclusion

Interest is growing in haemodialysis modalities beyond conventional three times weekly treatments. Small observational studies and a small randomized controlled trial suggest that nocturnal dialysis may provide better blood pressure control, reduce left ventricular mass and improve mineral metabolism. All of this suggests improved cardiovascular mortality for dialysis patients but does not prove it.

Conflict of interest statement. None declared.

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