Utility and Limitations of a Multicenter Nocturnal Home Hemodialysis Cohort

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Nocturnal home hemodialysis (NHD) is the most intensive dialysis strategy among dialytic renal replacement options and is receiving increased attention as more research reveals its physiologic restorative potential compared with conventional hemodialysis; however, a significant gap in knowledge remains concerning the predictors of program success and the clinical outcomes of NHD. This review aims to highlight the methodologic strengths and pitfalls of various study designs as they pertain to NHD research and lays the foundation for the CANandian Slow Long nightly ExtEnded dialysis Programs (CAN-SLEEP), a multicenter NHD research network aimed to facilitate investigation of NHD.

Clin J Am Soc Nephrol 3: 1846–1851, 2008. doi: 10.2215/CJN.00890208

Nocturnal home hemodialysis (NHD) is an intensive form of renal replacement therapy whereby patients self-administer their dialysis on 4 to 6 nights per week with each session lasting between 5 and 8 h. Thus, patients typically receive between 30 and 40 h of therapy per week, an amount significantly exceeding the 12 h routinely delivered with convention hemodialysis (CHD). Such augmented uremic clearance and ability to achieve more desirable fluid balance has prompted increasing interest in NHD in the past decade. As a result, the challenges of research in this area, particularly given the small number of centers that are able to provide this dialysis option to their patients, have been brought to the forefront. Our aim here is to consider the methodologic limitations relevant to the existing NHD literature and lay a framework for creating a multicenter collaborative NHD research network. The goal of this network is to establish a large NHD cohort to answer NHD-related research questions in a practical manner with sufficient power.

Methodologic Limitations of Existing Research

Although the constituent features of contemporary NHD (long duration, frequent treatments, nightly administration, and home based) are not novel, the NHD treatment strategy itself is the first to combine these four elements into a single modality. Uldall *et al.* (1) were the first to implement NHD in 1994, whereby patients underwent 8 h of home hemodialysis on 5 to 7 nights per week. Since then, interest in NHD has steadily increased for two primary reasons. First, there is mounting evidence that NHD is able to reverse many of the physiologic perturbations of uremia better than other forms of dialysis; and, second, evidence suggests that peritoneal dialysis (PD) and CHD have attained their maximum effectiveness and that relatively minor differences in small solute clearances, as assessed by urea Kt/V, miss the bigger picture that clearance of uremic toxins as achievable by conventional dialysis therapies is still grossly inadequate (2-5).

During the past decade, a small but growing body of literature has emerged to delineate the beneficial effects of NHD over CHD. These physiologic restorative properties of NHD have been discussed in detail elsewhere and were the subject of a recent systematic review (6-9). The majority of NHD research has been conducted by a small group of clinical research teams worldwide with a limited number of NHD patients. In fact, the number of patients who undergo home dialysis (either conventional home hemodialysis or NHD) is only approximately 1500 individuals in North America, a number that represents less than 0.5% of patients with ESRD; with few exceptions this low prevalence is typical of affluent Western countries (10). Thus, small sample sizes are the single most important barrier to addressing research questions with sufficient power to detect true differences between NHD and other forms of renal replacement therapies whether using randomized, controlled trials or relying on observational studies. Indeed, each study paradigm has its own advantages and disadvantages, which are briefly discussed.

Published online ahead of print. Publication date available at www.cjasn.org.

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ISSN: 1555-9041/306–1846

Experimental Studies (Randomized, Controlled Trials)

In a clinical setting, experimental studies are typically (although not exclusively) randomized, controlled trials whereby the effects of an intervention are measured on individuals who are randomly assigned either to receive or not to receive that intervention. These interventions may be as diverse as therapeutic agents, surgical procedures, risk factor modification, and educational programs, to name just a few examples. The strength of the randomization process is that the distribution of known and unknown confounders is presumed similar in all exposure groups at the outset of the trial, thereby minimizing the effect of this important bias in the interpretation of the link between the intervention under study and the outcome being ascertained (11,12). Thus, true experiments result in the strongest evidence for causation; however, for all of their methodologic strengths, randomized, controlled trials have a number of notable disadvantages, some of which are particularly relevant to NHD investigations. (*1*) Trials tend to be logistically complex and exceedingly costly, especially when involving more than a single center. This complexity relates not only to the randomization process itself but also to the planning phase; creating study protocols, manuals of operations and study forms; training of personnel; data collection, storage, and processing; patient screening, obtaining consent, and ensuring compliance; safety monitoring; and finally closing out the trial. (*2*) Because of the large sample sizes usually required to demonstrate differences in hard outcomes such as mortality, investigators often use surrogate outcomes that frequently have not been validated in specific disease populations (*e.g.*, ESRD). (*3*) Duration of follow-up frequently is not sufficiently long enough to discern beneficial or, more importantly, adverse outcomes. (*4*) Even in many well-conducted trials, patients tend to be a highly selected subgroup of the desired target population to whom the results of the study are hoped to be generalizable (this raises concerns of external validity). (*5*) Chance alone may result in imbalances of important baseline characteristics, particularly when the number of recruited patients is low. (*6*) Finally, it may be difficult to convince prospective trial participants of scientific equipoise, especially when practical issues or perceived convenience of one intervention *versus* another seem more germane to patients.

Several of these limitations are reflected in the only published randomized trial in the NHD literature as well as in the ongoing Frequent Hemodialysis Network (FHN) trial. In the former, 52 individuals were randomly assigned to receive either home NHD (5 or 6 nights/wk, minimum 6 h/session) or conventional in-center or home hemodialysis (3 sessions/wk, 4 h/session); the primary outcome was change in left ventricular mass (LVM) at 6 mo as assessed by cardiovascular magnetic resonance imaging (13). Although this trial did show a benefit of NHD on LVM, a surrogate outcome assumed (but not proved) to portend improved cardiovascular mortality (14,15), the effects on a number of secondary outcomes, including quality-of-life measures, were more modest. Given that only 25 and 27 patients were randomly assigned to each treatment arm also increases the likelihood that important confounders were unequally distributed between the treatment groups despite randomization. Although not an intended criticism of the study, it does highlight some of the aforementioned limitations, particularly as these pertain to a small sample size, even in a well-planned and executed trial. The FHN study, a National Institutes of Health– and Centers for Medicare and Medicaid Services–funded randomized trial of NHD *versus* CHD, to which our own groups contribute, has estimated a sample size of 125 patients per treatment arm to yield a clinically relevant result; however, even recruiting this number of patients is proving to be extremely challenging despite involving 19 centers across the United States and Canada. This trial demonstrates the logistical complexity of coordinating many sites and is itself very unlikely to complete recruitment, follow-up, and close-out within the intended time frame (16). Recruitment challenges have centered around patients' unwillingness to be randomly assigned to a perceived inferior therapy (conventional dialysis) when an alternative is available. The primary outcome is a composite of 1-yr mortality (a hard outcome) and change in LVM (a surrogate outcome) or 1-yr mortality and change in health-related quality of life (16). In fact, if mortality alone were the desired outcome, then a prohibitive 5000 patients would have to be randomly assigned to have 90% power to detect a 30% reduction in mortality (17). Although we certainly encourage the conduct of desperately needed trials, given the current gap in knowledge and the limited amount of available resources, randomized trials alone are not a practical means to address many important research questions relating to NHD outcomes.

Quasi-experimental Studies

The majority of published NHD research is based on quasi-experimental studies. In this paradigm, the investigator studies patients who are nonrandomly assigned to a particular intervention or takes advantage of a change in patients' state to investigate the effect of this change in state on a health outcome (18). In the NHD literature, the intervention is typically NHD, and the change in state refers to the conversion from CHD to NHD. The study model is usually a before-and-after paradigm; frequently, a comparator group (an external control) that does not undergo the conversion to the alternative modality is added to enhance the internal validity of the study. Some relevant health parameter, such as LVM, phosphate binder use, hemoglobin concentration, or sleep pattern, is then studied while a patient is undergoing CHD and assessed again after some time interval while on NHD (19-22). The presumption is that any change observed between measurements is due to the nocturnal dialysis. Because patients serve as their own internal control, this approach seems particularly well suited for investigations with small sample sizes; however, a number of limitations to quasi-experimental studies must be considered when tempted to ascribe causation for a change in outcome to NHD. These are outlined in detail elsewhere (18) and are summarized in Table 1. Numerous examples from the NHD literature demonstrate these limitations. A number of studies using the quasi-experimental paradigm have reported parathyroid hormone levels before and after conversion to NHD (23-25). Although all studies demonstrate a reduction in parathyroid hormone with

Table 1. Advantages and disadvantages of quasi-experimental studies

Advantages	Disadvantages
Conceptually simple before-and-after designs with or without external controls	Secular trends in treatment may affect outcome independent of the intervention
Better suited for small sample sizes	Passage of time may interfere with presumed exposure/intervention and outcome relationship
	Repeated assessment of the same individual familiarizes patients with instruments and may change behavior
	Regression to the mean may minimize extreme preintervention values unrelated to the intervention itself
	Potential selection bias if external control group not the same as the intervention group
	Potential selection bias if loss to follow-up, dropouts, or attrition is different between comparator groups
	Rigorous timing of outcome ascertainment must be ensured

NHD, these changes are not statistically significant and are complicated by unavoidable co-interventions, such as changes in diet, phosphate binder use, serum phosphate levels, or dialysate calcium concentrations, all of which can influence secondary hyperparathyroidism. The role of NHD in reversing hyperparathyroidism thus remains confounded and must be interpreted with caution. Although a number of design features may mitigate the pitfalls of quasi-experimental designs (18), biases are difficult to control completely and differ with respect to the research question and study method: questionnaires that explore quality of life before and after conversion to NHD are inherently different from studies that investigate gene expression as a result of conversion and are prone to different limitations.

Observational Studies

This paradigm includes case reports or case series, cross-sectional studies, case-control studies, and cohort studies. The advantages and disadvantages of each approach, with accompanying examples from the nephrologic literature, were recently reviewed elsewhere (26). Case-control studies are not represented in the NHD literature and are not considered further here.

Case reports and case series typically describe a unique clinical predicament concerning the diagnosis, prognosis, or treatment of a single individual or small group of patients. There are no control patients in this study design, and observed outcomes may be due to regression to the mean or result from chance alone, in addition to the hypothesized mechanism. These studies are generally inappropriate for population-level inference but can bring an unusual clinical experience to the attention of a broader audience and facilitate future hypothesis generation. This is not to say that case reports/series cannot be informative; the recent series of five successful pregnancies among a total of 45 women who were of child-bearing age and on NHD between 2001 and 2006 is certainly a strong endorsement for the role of NHD in reversing the amenorrhea and infertility that typically are associated with ESRD (27).

A number of cross-sectional studies have also been reported in the NHD literature. These are usually in the form of surveys such as the recent study comparing health-related quality of life and illness intrusiveness among NHD and PD (28). The advantage of cross-sectional studies is that they are relatively inexpensive, conceptually simple, and particularly good at determining the prevalence of a health state in a population; however, because both the proposed exposure (*e.g.*, NHD) and the presumed outcome (*e.g.*, quality of life) are assessed at the same point in time, their temporal relationship is uncertain: does NHD lead to a good quality of life, or does a good quality of life result in choosing NHD as a treatment modality? Additional biases may arise when the respondents of a survey differ systematically from nonrespondents (a type of selection bias referred to as responder bias). Thus, these studies are also only hypothesis generating.

Cohort studies represent the last major study design for consideration in this review. At present, few NHD programs worldwide include more than 75 patients, suggesting that cohorts that are large enough to yield meaningful research results are rare. Notwithstanding this obvious shortcoming, cohort studies offer potential advantages for future NHD research. They are relatively inexpensive compared with randomized trials, are ideal for uncommon exposures (at present, NHD may be considered a rare exposure), and can test several hypotheses in the context of the same cohort because multiple effects of a single exposure can be investigated simultaneously (*e.g.*, mortality, hospitalizations, technique survival, cardiac geometry, quality of life, nutritional effects). Cohort studies also tend to include a broader spectrum of patients as compared with the frequently restrictive inclusion/exclusion criteria of trials. An additional advantage of longitudinal cohorts (whereby multiple measurements are made at prescribed time intervals) is the insights gained into etiologic, prognostic, and natural history factors where randomization may be impossible or unethical.

Although a large number of reports in the NHD literature identify themselves to be observational cohort studies, they are,

in fact, variations of quasi-experimental paradigms (before and after conversion to NHD) with or without external controls and are subject to limitations of that study design. To our knowledge, the only true NHD cohort (not cohort *study*) that has been described is the International Quotidian Dialysis Registry in which our own centers participate. This registry, established in 2004 and now involving eight countries, aims to collect valuable data on mortality, transplantation, hospitalizations, and modality change (29). To date, however, no study has been published using this cohort, and currently available data are purely descriptive (30). Limitations of future cohort studies derived from this data set, as with all NHD cohort studies, have been previously outlined (29). Most important, these include the potential for selection bias (given that patient recruitment to NHD is not a random occurrence, and self-selection or referral bias is likely a significant determinant), information bias (particularly pertaining to data reliability and accuracy), and confounding (requiring a high degree of patient-level detail to adjust for as many potential confounding variables during analysis). A specific type of selection bias that warrants special mention in the context of cohort studies is incidence-prevalence bias. Inclusion of prevalent patients may introduce systematic error tending to favor the group with more prevalent patients because these individuals tend to have more advantageous characteristics compared with incident patients as evidenced by the fact they have survived long enough to be studied. Although we contribute to and support the International Quotidian Dialysis Registry and believe that this initiative will be able to address broad population-level issues of practice patterns and outcome trends, it is less well suited to address specific questions that require a very high degree of data granularity and integrity.

Creating a Multicenter Collaborative NHD Network

With all major research paradigms having desirable and undesirable features, is there a mechanism to advance the domain of NHD research in a timely, practical, and cost-effective manner? We believe that one solution lies in the creation of a uniformly developed NHD cohort with internal consistency and detailed, high-quality, patient-level data that allow investigators to interrogate NHD with a higher degree of precision than is currently possible. To that end, our groups have joined together to create a multicenter NHD research network that brings together approximately 350 to 400 retrospective and concurrent NHD patients across four Canadian centers into a single cohort. Called CANadian Slow Long nightly ExtEnded dialysis Programs (CAN-SLEEP), the immediate goal is a description of NHD across our centers in an effort to benchmark outcomes. Our long-term goal is to plan cohort studies by matching the CAN-SLEEP cohort to patients who have ESRD and are receiving other renal replacement therapies at our centers.

In regard to benchmarking NHD outcomes, we have identified a number of high-priority areas that are anticipated to be of broad interest in advancing the domain of NHD. These include defining NHD technique survival and characterizing factors that are associated with long-term success, cataloguing vascular access outcomes with attention to thrombotic and infectious complications, and tracking longitudinal changes in quality of life among patients who receive NHD.

Consideration has been given to the aforementioned limitations in the eventual planning of cohort studies that use the CAN-SLEEP cohort, and a framework for mitigating these barriers has been proposed (Figure 1, Table 2). (*1*) The sharing of data among our programs brings a substantial NHD population under a single umbrella, thereby optimizing the power to detect true outcome effects of NHD as well as prognostic factors of modality success. (*2*) Uniform definitions of exposures and outcomes will be applied across all participating centers, thereby maximizing data quality and minimizing information bias. (*3*) Prospective collection of data minimizes information bias and possible confounding by variables that can be defined *a priori* to ensure adequate collection of quality data. (*4*) By virtue of NHD's having a captive patient population dependent on care from a very limited number of referral centers, losses to follow-up are virtually nonexistent in this population. This maximizes the amount of outcome information that can be obtained on patients without disadvantageous selection-out bias. (*6*) Uniform electronic data storage across study sites will facilitate secure and easy access to collected information, allowing efficient translation of raw data into research results and

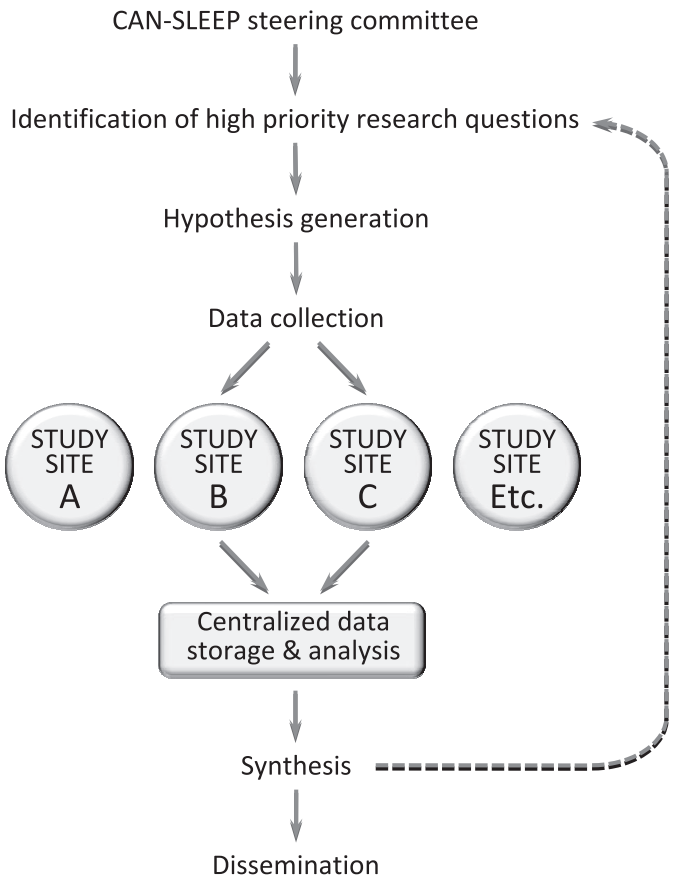

Figure 1. Structural framework of the CANandian Slow Long nightly ExtEnded dialysis Programs (CAN-SLEEP) network.

Table 2. Desirable design features of the CAN-SLEEP cohort[a]

Design Feature	Benefit
Merge data from multiple Canadian NHD programs into a single cohort	Increases sample size and maximizes power
Hypothesis driven, research question oriented	Avoid data dredging, maintain focus of network priority
Uniform definitions of exposures and outcomes across centers	Maximizes data quality and minimizes information and selection biases
Minimal loss to follow-up with captive NHD population to maximize outcome information	Minimizes selection bias
Prospective collection of data on a variety of themes	Minimizes information bias and confounding
Uniform electronic record keeping	Minimizes information bias by ensuring data integrity and uniform storage of patient-level data
Restriction to incident patients where possible	Minimizes selection bias and confounding

[a]CAN-SLEEP, CANandian Slow Long nightly ExtEnded dialysis Programs; NHD, nocturnal home hemodialysis.

ultimately clinical practice. (*7*) All future cohort studies derived from this population will be hypothesis driven and address specific research questions in an effort to minimize retrospective data mining and the associated risk of information bias.

The creation of this unique cohort will allow us to address a more narrow scope of research questions that are less well suited for large international registries in which the type of data and their granularity are inherently different than for a highly structured cohort with greater microscopic data detail. Thus, we see this initiative as complementary to the International Quotidian Dialysis Registry, to which we continue to contribute. Because many NHD-related research questions (*e.g.*, technique survival or infectious complications) are not amenable to randomized trials, the CAN-SLEEP endeavor does not overlap with the ongoing FHN initiative.

Conclusions

Interest in NHD has accelerated with the realization that traditional forms of CHD and PD have likely plateaued in their ability to positively affect ESRD morbidity and mortality, combined with an emerging body of literature documenting the physiologic restorative properties of NHD. Encouraging as this form of renal therapy may be, broad-based adoption and public payer underwriting will be greatly aided by a new tack on NHD investigation with the creation of a multicenter NHD cohort to address globally relevant research questions in an efficient manner. The long-term goal is to establish evidenced-based clinical practice guidelines to facilitate standardization of NHD care, which will allow renal care providers to administer the best possible state-of-the-art dialysis to their patients.

Acknowledgments

We thank the ongoing dedication of the staff of the NHD programs of the Toronto General Hospital, Humber River Regional Hospital, British Columbia Renal Agency, and the University of Alberta Hospital. We thank Dr. Marcello Tonelli for insightful editorial suggestions.

Disclosures

None.

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