The effect of extended hours dialysis on sleep quality in a randomised trial

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Running title: Effect of Extended Hours Dialysis on Sleep

Abstract

Background

Poor sleep quality is common in haemodialysis patients and associated with worse outcomes. In this pre-specified analysis, we examined the impact of extended hours haemodialysis on sleep quality.

Methods

The ACTIVE Dialysis trial randomized 200 participants to extended (≥24 hours/week) or standard (target 12-15 hours) hours haemodialysis over 12 months. Sleep quality was measured in the Kidney Disease Quality of Life Short Form 1.3 (KDQOL-SF) by overall sleep quality score (0-10, 10 = "very good") and the sleep subscale (0-100, 100 = 'best possible sleep') every three months via blinded telephone interviewer. The average intervention effect was calculated by mixed linear

regression adjusted by time point and baseline score. Factors predicting sleep quality were assessed by multivariate regression analysis.

Results

Overall sleep quality score and sleep subscale at baseline were similar in both groups (5.9 [95%CI 5.4-6.4] vs 6.3 [5.9-6.8]; 65.0 [60.9-69.1] vs 63.2 [59.1-67.3]; extended and standard hours respectively). Extended hours haemodialysis led to a non-significant improvement in overall sleep quality score (average intervention effect 0.44 (-0.01-0.89), p=0.053) and sleep subscale (average intervention effect 3.58 (-0.02-7.18), p= 0.051). Poor sleep quality was associated with being female and with current smoking. Sleep quality was positively associated with EuroQol-5D (EQ5D) and the SF-36 Physical Component and Mental Component Summary Scores but not with hospitalisations.

Conclusions

Sleep quality was not significantly improved by extended hours dialysis in this study. Sleep quality is positively correlated with quality of life in haemodialysis patients and is poorer in women and current smokers.

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Registration: ClinicalTrials.gov registry (NCT00649298)

Introduction

Poor sleep quality and daytime sleepiness are reported to affect 20-83% of patients with end-stage renal disease (ESRD) treated with dialysis[1, 2]. There are multiple postulated causes for this, including sleep apnoea, restless legs syndrome (RLS) and symptoms of kidney disease[2-4]. Previous studies have highlighted that poor sleep is associated with increased mortality and poor quality of life[2, 5, 6]. Patients place high importance on sleep, with the prospect of better sleep substantially more likely to induce them to extend their dialysis hours than the prospect of lengthened life expectancy[7].

The impact of extended hours haemodialysis on sleep quality is uncertain. Short daily haemodialysis six times per week has been associated with reduced symptoms of RLS and sleep improvements[8] while extended nocturnal haemodialysis 6-7 nights per week has been associated with improvements in obstructive sleep apnoea[4]. However, two previous randomised-controlled trials did not show an improvement in subjective sleep quality with frequent dialysis (5-6 times per week) compared to standard thrice weekly dialysis[9, 10].

The ACTIVE Dialysis trial randomised 200 participants to extended or standard hours haemodialysis for 12 months resulting in a doubling of weekly haemodialysis hours (median weekly hours 24.0 (inter-quartile range (IQR) 23.6, 24.0) versus 12.0 (IQR 12.0, 16.0) in the extended and standard groups respectively. The intervention had no effect on the primary outcome of quality of life at 12 months as measured by EuroQol-5D-3L (EQ5D) (mean difference 0.037, 95% CI 0.032, 0.105, p=0.29). However, there was a small, statistically significant improvement in Physical Component Summary (PCS) and Mental Component Summary (MCS) of 2.30 (95% CI 0.53-4.07, p=0.01) and 2.54 (95% CI 0.42-4.65, p = 0.02) points respectively[11].

In an analysis planned before the ACTIVE Dialysis study was completed, we aimed to investigate whether randomisation to extended haemodialysis hours improved self-reported sleep parameters and to examine the factors that predicted sleep quality in the ACTIVE Dialysis trial population.

Methods

Study Design

The ACTIVE Dialysis trial randomised 200 participants from 40 sites across four countries to extended or standard hours haemodialysis between August 2009 and July 2013. It is the largest completed, randomised controlled trial investigating the impact of extended weekly haemodialysis hours. The design, baseline characteristics[12] and primary results[11] of the ACTIVE Dialysis trial have been previously reported. In brief, this international, multicentre, open-label, blinded endpoint-assessment trial randomised participants from both in-centre and home-based haemodialysis programs in Australia, Canada, China and New Zealand to receive either extended (≥24 hours) or standard (≤18 hours) haemodialysis over a minimum of three sessions per week for 12 months. The location and timing of dialysis (home or institution, nocturnal or daytime) was not specified and left to the discretion of the patient and treating physician. Eligibility criteria included age >18 years, life expectancy >6 months, not planned to receive a renal transplant within twelve months and not currently treated with extended hours haemodialysis. Consenting participants were randomized in a 1:1 ratio via a central, web-based interface using a minimisation algorithm and stratified according to geographical region (Australia/New Zealand vs China/Canada), dialysis setting (institution vs home), and dialysis duration at study entry (≤6 months vs >6 months). Participants and physicians were not blinded to study allocation; however endpoints were assessed in a blinded fashion. Participants were followed for 12 months unless they died, withdrew consent or were transferred to a setting that could not offer both therapies. Participants unable or unwilling

to adhere to randomized treatment continued to participate in planned study assessments to allow intention-to-treat analyses.

Measures

The primary outcome of the current analysis was the average intervention effect on the overall sleep quality score. Participants completed a number of questionnaires at baseline and every three months during follow up via a telephone interview conducted by study personnel blinded to the randomised allocation. The interview questionnaires included the Kidney Disease Quality of Life Short Form Questionnaire (KDQOL-SF 1.3) which incorporates the items from the SF-36 and 43 questions relating to kidney disease[13]. Four of these relate to sleep; the first determines the overall sleep quality score by asking participants to rate this on a scale with 0 representing "very bad" and 10 "very good". In addition, three subsidiary questions ask how often over the past four weeks did they 1) "Awaken during the night and have trouble falling asleep again?" 2) "Get the amount of sleep you need?" and 3) "Have trouble staying awake during the day?" These answers are rated on a six point Likert scale with responses ranging from "none of the time" to "all of the time". The answers to all four items are then scaled, producing the KDQOL sleep subscale ranging from 0-100 with higher scores indicating better sleep[13]. The KDQOL sleep subscale has been shown to have good internal consistency, reliability and validity[14, 15] and has been correlated with other measures of health related quality of life[5].

Primary and Secondary Outcome

For these analyses, we selected the overall sleep quality score as our primary outcome given its correlation with mortality in previous studies[2, 5]. We also report the KDQOL sleep subscale which has a demonstrated strong correlation with dedicated sleep-quality questionnaires such as the Pittsburgh Sleep Quality Index (PSQI)[15].

Statistical analysis

Data is presented as means and standard deviation (SD) for normally distributed variables and median and interquartile ranges (IQR) when non-normally distributed. Comparison of means and medians were performed using the Student's t-test or the Mann-Whitney U test where appropriate. All analyses were conducted on an intention-to-treat basis assessing the average intervention effect from each follow up visit for the difference between the two intervention groups. All participants were included in the analysis regardless of whether dialysis was nocturnal or diurnal. Average intervention effect was estimated from a mixed linear regression model incorporating time point and baseline score. No imputation was performed for the missing data points. Generalised estimating equation modelling (incorporating variables specified *a priori* for hypothesised impact on sleep scores: total dialysis hours per week, age, gender, time on dialysis (≤6 months or >6 months), dialysis location, smoking status, number of co-morbidities, body mass index and baseline EQ5D score) was used to predict self-reported overall sleep quality and, separately, to define the relationship with quality of life measures. The association of baseline overall sleep quality score with risk of hospitalisation during the intervention period was also investigated using logistic regression. Statistical analyses were performed using SAS Enterprise Guide 5.1 (SAS Institute Inc.).

Ethics

The ACTIVE Dialysis clinical trial was approved by the Human Research Ethics Committee of Northern Sydney Central Coast Health, NSW, Australia (HREC/09/HARBR/26) and each centre obtained additional approval in accordance with local requirements. The trial is registered at clinicaltrials.gov (NCT00649298). All patients provided written, informed consent.

Results

Baseline results

Baseline characteristics are shown in Table 1. The median weekly dialysis hours in the extended group was 24 hours (IQR 24,24) compared with 12 hours (IQR 12,16) in the standard group. Nocturnal dialysis comprised a portion or the entirety of weekly dialysis hours for 14% of follow up visits in the extended hours group and 5% in the standard hours group (Table S1). KDQOL sleep domain responses were available for a minimum of 82% of participants at each time point. Mean baseline overall sleep quality score was 6.1 (95%CI 5.8-6.5) and the mean sleep subscale score was 64.1 (95%CI 61.2-67.0). There were no significant baseline differences in mean scores on overall sleep quality score or any of the three subsidiary questions (Table S2).

Effect of Randomisation

There was no significant interaction between time and intervention effect on either measure of sleep quality (results not shown). Both the primary outcome of overall sleep quality score and the secondary outcome of sleep subscale score increased from baseline in the extended hours group while remaining unchanged in the standard hours group. However, these differences did not reach statistical significance and were not apparent at the final time point. Over the duration of the trial, no significant average intervention effect was apparent in overall sleep quality (0.44, 95%CI -0.01-0.89, p=0.053) (Figure 1a) or sleep subscale (3.58, 95% CI -0.02-7.18, p=0.051) (Figure 1b, Table S3). The results were similar for the three subsidiary questions (Table S2).

Factors impacting on sleep quality

Regression analysis demonstrated female gender and current smoking status to be predictors of poor overall sleep quality score. A positive association with quality of life as measured by EQ5D (Table 2) was also seen. When considered individually, EQ5D, PCS and MCS all correlated with overall sleep quality score (Table 3). When adjusted for age, gender and treatment allocation, nocturnal dialysis had no impact on overall sleep quality, although the number of participants practising nocturnal dialysis was small (Table S4). Post-hoc observational analyses demonstrated a significant positive relationship between total weekly dialysis hours and overall sleep quality that remained

after adjustment for baseline overall sleep quality, age, gender and smoking status (p=0.04)(Table S5). This result should be interpreted with caution given the exploratory nature of the analyses.

Associations of outcomes with baseline sleep quality

Hospitalisation was inversely associated with overall sleep quality (odds ratio 0.85; 95%CI 0.73-0.98; p=0.03) in univariate analysis although the association disappeared after adjustment for confounders (OR 0.89, 95%CI 0.76-1.04; p=0.14) (Table S6).

Discussion

Extended dialysis did not have a significant effect on sleep quality in the ACTIVE Dialysis trial; either for the overall sleep quality score, the sleep subscale or its individual component questions. The average treatment effect of extended hours dialysis approached statistical significance for both overall sleep quality score (p=0.054) and sleep subscale score (p=0.051) and it is possible that the lack of a clear difference was due to inadequate power, as this trial was not powered specifically to assess sleep. Nonetheless, the effect would need to be much larger than that observed in this trial to normalise sleep satisfaction.

Our population reported better sleep quality than the general haemodialysis population[2] where the mean overall sleep quality score and sleep subscale score has been estimated at 5.5– 5.8[2, 5] and 58.7[16] respectively. This may be explained by selection bias where participation in a randomized trial of extended hours dialysis is likely to have led to a substantial underrepresentation of patients with a higher co-morbidity burden. Additionally, our trial cohort was relatively younger than the general haemodialysis population[12, 17]. However, the sleep quality of the present cohort remains poor with the mean baseline sleep subscale score in our cohort of 64.1 falling substantially below the threshold of 76 identified (with reference to the well-accepted Pittsburgh Sleep Quality Index)

as indicative of poor quality sleep in dialysis patients[15]. The results further highlight the problem of poor sleep in dialysis patients.

There is no accepted agreement on what difference in sleep subscale score or overall sleep quality score represents a clinically meaningful difference (as distinct from a statistically significant difference). There are multiple ways to address this general issue, including distributional approaches based on comparing the size of the between group difference to the variation within the population as a whole or attempts to anchor differences in score with accepted clinically meaningful events. A simple and commonly applied distributional approach calculates the ratio of the effect size to the population standard deviation (a value known as Cohen's d) and suggests that effect sizes be thought of as <0.2 (small), 0.2-0.5 (moderate) and >0.5 (large)[18]. In the case of the present study, this results in values of 0.18 and 0.17 (for overall sleep quality and sleep subscale scores, respectively) suggesting that any effect present is, at best, small. Moreover, the average intervention effect we observed on the sleep subscale (3.6) was only a fraction of that required to lift the average sleep subscale score of 64.1 out of the 'poor quality' range, raising further uncertainty as to the clinical significance of the effect seen.

Previous studies have produced conflicting results on factors associated with poor sleep in dialysis populations. Multiple factors have been shown to affect sleep quality. Female gender and current smoking are inconsistently associated with lower quality sleep[2, 5, 19]. Nicotine is known to cause poor sleep latency, sleep fragmentation and reduced sleep efficiency[20], and as data on comorbid respiratory disease was not available in the ACTIVE study, residual confounding from smoking-related respiratory disorders cannot be excluded in the present analysis. The influence of gender on sleep is undoubtedly complex. Sleep disturbance is a more common manifestation of depression amongst women than men and depression is common in patients with ESKD[1, 21]. It is possible that the observed gender imbalance in sleep quality in the present study at least partly reflects differing symptoms of depression. Mental health issues such as depression and anxiety can themselves contribute to poor sleep quality as can the use of associated medications such as hypnotics. While

we were not able to directly assess the effect of depression or anxiety, we were able to demonstrate a positive association with quality of life as measured by the EQ-5D instrument. We were not able to test the impact of hypnotics. An association between age or BMI and sleep quality is not consistently found in previous studies[2, 5] and was also not evident in participants of the ACTIVE study. We did find an association between poor sleep and poor quality of life, including both lower PCS and MCS, similar to multiple previous studies[6, 15].

Earlier studies have not shown correlation of sleep quality scores with urea clearance (Kt/V)[6] nor significant improvement in sleep quality with increasing Kt/V or with the use of a high-flux membrane[22]. However, observational studies have reported a positive association between more frequent and/or extended weekly hours dialysis (a state of improved molecular clearance) and sleep quality[4, 8]. These positive associations contrast with the negative results from three previous randomised controlled trials reporting on sleep outcomes with frequent or extended dialysis and sleep. Neither the FHN Daily Trial of increased session frequency nor the FHN Nocturnal or Alberta trials of frequent nocturnal haemodialysis found an impact on sleep quality[9, 10]. The present trial differs from these trials in that the intervention was achieved mainly by lengthening the duration of dialysis sessions while maintaining a thrice-weekly dialysis frequency and in that there were few participants performing nocturnal dialysis. The results of ACTIVE would be consistent with the hypothesis that sleep quality can be improved through a dialysis prescription that increases clearances beyond that of routine dialysis but avoids the physiological and cognitive demands of nocturnal dialysis. However, a cautious interpretation is warranted for a number of reasons. We did not observe an interaction between nocturnal dialysis and the effect of treatment on sleep quality, although the ability to detect a difference is likely to have been limited by the small sample size of those dialysing at night. Also, the absolute difference in sleep quality between the two groups in the present study was not large and, as in the FHN trials[10], appears to narrow at the final visit for reasons that were not apparent (despite treatment adherence remaining stable through the duration of the trial[11]). Thus, the hypothesis that extended hours dialysis improves sleep quality remains

speculative until further evidence distinguishing the impact of daytime versus night-time dialysis on sleep emerges.

The pathophysiology of sleep disorders in dialysis patients is complex and multifactorial. Objectively measured reductions in sleep quality are evident in patients with chronic kidney disease and more severe disturbances are seen in dialysis patients[23]. Mean polysomnography parameters are markedly abnormal in dialysis patient cohorts, even after excluding patients with chronic conditions or medications that may contribute to poor sleep quality. Parameters including total sleep time, sleep latency, REM latency, brief arousal index, periodic leg movement index and sleep efficiency are markedly worse in dialysis patients compared to healthy controls[23].

Concomitant pathology such as uraemic pruritus, RLS and peripheral neuropathy may all directly disturb the sleep of patients with advanced renal disease[5, 6]. Furthermore, comorbid obstructive sleep apnoea and congestive heart failure are more common and both are associated with poor sleep quality. These pathologies interact adversely to worsen sleep quality. Hypervolaemia causing pharyngeal oedema is a postulated exacerbator of obstructive sleep apnoea[24] while correction of fluid overload by dialysis has been shown to reduce apnoea-hypopnoea index in haemodialysis patients with OSA[24]. Chronic metabolic acidosis and the rapid shifts in cerebrospinal pH following dialysis are thought to affect central respiratory drive and contribute to the increased prevalence of central sleep apnoea in dialysis patients[25]. Hypocapnia due to respiratory compensation for metabolic acidosis interacts with co-existing fluid overload to destabilize respiratory control[25]. These mechanisms have been postulated to explain the findings of observational studies showing improvements in apnoea-hypopnoea index in haemodialysis patients changed from standard dialysis to frequent nocturnal dialysis[4] and the association between lower serum bicarbonate and poorer sleep quality[26]. However, the relationship between serum bicarbonate and sleep may be complex as metabolic acidosis may actually improve central sleep apnoea but worsen obstructive sleep apnoea by inducing stronger diaphragmatic and thoracic muscle action in the setting of poor pharyngeal tone[27]. More recently, dysregulation of circadian rhythm has emerged as a potential important

contributor to poor sleep in patients with end-stage kidney disease. Patients on haemodialysis demonstrate suppression of the normal diurnal variation in melatonin and cortisol levels and marked alterations in peripheral expression of circadian clock gene mRNA. It is hypothesised that impaired clearance of centrally derived mediators of circadian rhythm leads to the loss of effective circadian signalling to peripheral tissues[28]. The complex interaction between poor sleep, multiple co-morbidities and overall health may explain the correlation between adverse changes in biochemical parameters including albumin, haemoglobin and phosphate and sleep quality[6, 23, 29].

The optimal treatment for sleep disorders in haemodialysis patients is not known. Multiple interventions have shown promise in small, short-term studies, including melatonin, cognitive behavioural therapy, exercise training, correction of anaemia and acupressure[30, 31]. Additionally, treatment of sleep-disturbing conditions such as RLS, uremic pruritus and peripheral neuropathy has been associated with improvement in sleep quality[32-34].

The strengths of this study are our use of repeated measurements using a reliable, validated measure of sleep quality over the 12-month study period. The ACTIVE trial enrolled a diverse population, increasing the generalisability of the results. However, the relatively young mean age of participants confirms that (as is usual for extended hours or home dialysis studies) older and frailer patients were not well represented meaning caution is required in generalizing the results to those patient populations. Similarly, most of our participants performed dialysis during daylight hours and so our results may not be generalizable to nocturnal dialysis. The main limitation of the study is its relatively small size. Also, we did not use a dedicated sleep assessment tool such as the PSQI[15], Medical Outcomes Study Sleep Problems Index[10], a sleep diary, nor a direct measure of sleep metrics such as polysomnography. However, the KDQOL sleep subscale has been shown to correlate with the PSQI[15]. The advantages of the KDQOL sleep section in studies where sleep assessment is not the primary objective are the relative simplicity of use and its incorporation in a larger questionnaire, capturing other valuable quality of life data[15]. We were also unable to adjust for other potential confounders such as anxiety and depression or the use of hypnotic medications.

Conclusion

Dialysis patients suffer high rates of sleep problems and improving sleep quality is an important priority. Extended hours haemodialysis did not significantly improve sleep quality in this randomised controlled trial. Sleep quality is positively correlated with quality of life in haemodialysis patients and is poorer in women and current smokers.

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Figure 1: Sleep quality by treatment group over time

Mean overall sleep quality score (range 0-10) (A) and sleep subscale score (range 0-100) (B) over the duration of the trial by treatment group. Higher scores indicate better sleep. Average intervention effect estimated from mixed linear regression adjusting for baseline score and visit.

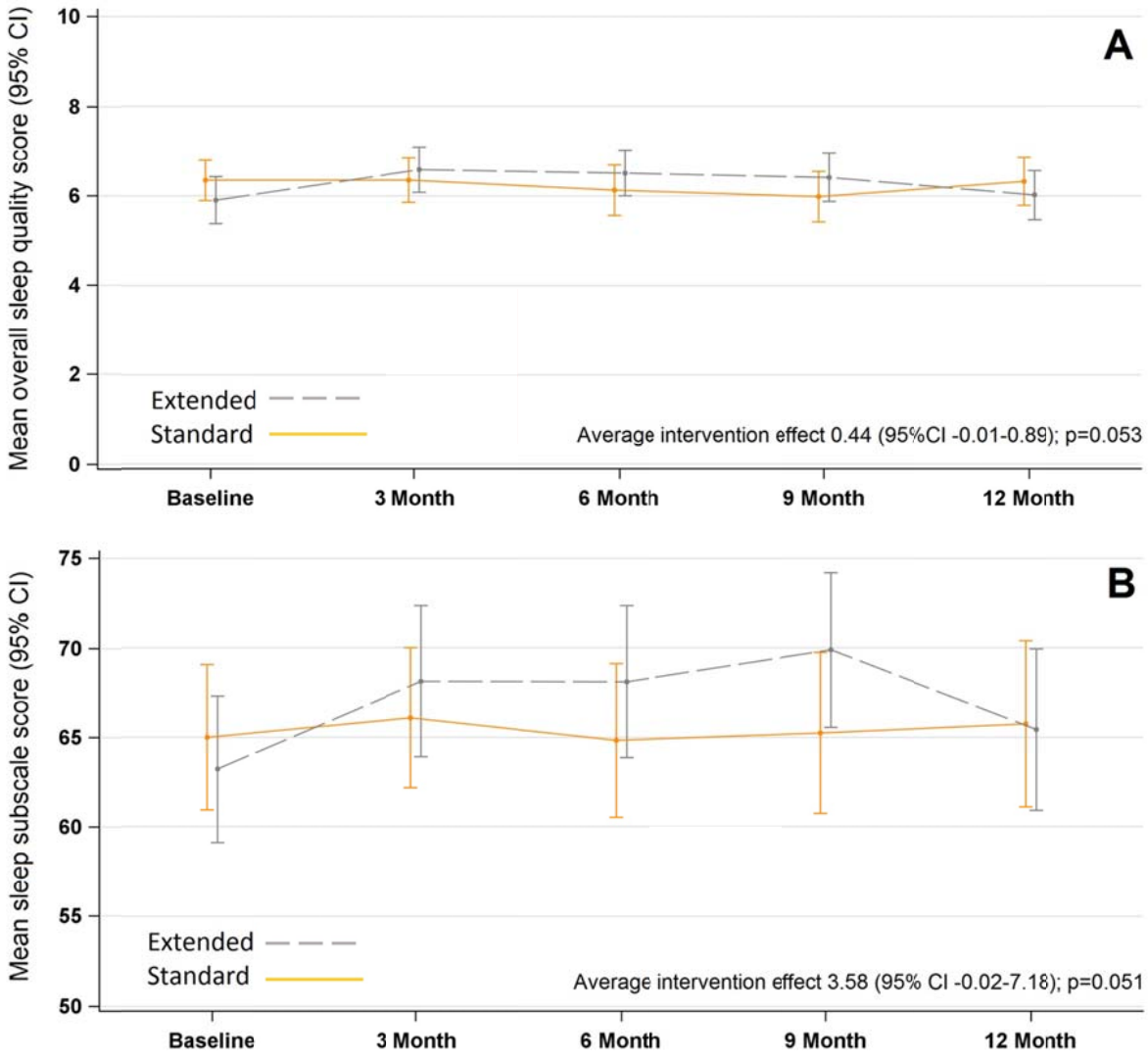

Table 1: Baseline patient characteristics

Characteristics	Standard (N = 100)	Extended (N = 100)	Total (N = 200)
Mean age at randomisation (SD)	51.6 (11.50)	52.1 (12.72)	51.8 (12.10)
Male (%)	70 (70.0%)	69 (69.0%)	139 (69.5%)
Primary cause of renal disease			
Diabetic Nephropathy	34 (34.0%)	27 (27.0%)	61 (30.5%)
Hypertension/Vascular Nephrosclerosis	11 (11.0%)	11 (11.0%)	22 (11.0%)
Glomerulonephritis	34 (34.0%)	41 (41.0%)	75 (37.5%)
Reflux Nephrology	5 (5.0%)	3 (3.0%)	8 (4.0%)
Polycystic Kidney Disease	7 (7.0%)	5 (5.0%)	12 (6.0%)
Other or unknown	9 (9.0%)	13 (13.0%)	22 (11.0%)
Smoking status			
Never smoked	56 (56.0%)	60 (60.0%)	116 (58.0%)
Past cigarette smoker	23 (23.0%)	20 (20.0%)	43 (21.5%)
Current cigarette smoker	21 (21.0%)	20 (20.0%)	41 (20.5%)
Diabetes Mellitus	39 (39.0%)	34 (34.0%)	73 (36.5%)
Congestive Cardiac Failure	13 (13.0%)	19 (19.0%)	32 (16.0%)
Country			
Australia	28 (28.0%)	30 (30.0%)	58 (29.0%)
Canada	6 (6.0%)	5 (5.0%)	11 (5.5%)
China	62 (62.0%)	62 (62.0%)	124 (62.0%)
New Zealand	4 (4.0%)	3 (3.0%)	7 (3.5%)
Ethnicity			
Asian	60 (60.0%)	58 (58.0%)	118 (59.0%)
Caucasian	23 (23.0%)	22 (22.0%)	45 (22.5%)
Other	17 (17.0%)	20 (20.0%)	38 (18.5%)
Number of dialysis sessions per week			
2	1 (1.0%)	1 (1.0%)	2 (1.0%)
3	82 (82.0%)	86 (86.0%)	168 (84.0%)
4 or more	17 (17.0%)	13 (13.0%)	30 (15.0%)
Mean total number of hours on dialysis per week (SD)	14.1 (2.8)	13.6 (2.6)	13.9 (2.7)
Duration on dialysis at enrolment, median (IQR) in years	2.63 (0.97, 6.74)	2.43 (0.67, 5.04)	2.48 (0.72, 6.00)
Intended Dialysis site for study treatment			
Home	25 (25%)	26 (26%)	51 (25.5%)
Institution	75 (75.0%)	74 (74.0%)	149 (74.5%)
Nocturnal dialysis (all or part of weekly dialysis performed at night)	6 (6.0%)	4 (4%)	10 (5.0%)

Characteristics	Standard (N = 100)	Extended (N = 100)	Total (N = 200)
Body Mass Index, median (IQR) in kg/m^2	24.9 (22.5, 29.3)	24.3 (21.2, 27.9)	24.5 (21.9, 29.0)
EQ5D, mean (SD)	0.76 (0.25)	0.79 (0.23)	0.78 (0.24)
Sleep quality scores from KDQOL-SF, mean (SD)			
Overall Sleep Quality	6.3 (2.31)	5.9 (2.67)	6.1 (2.50)
Sleep Subscale	65.0 (20.71)	63.2 (20.83)	64.1 (20.74)

Table 2: Factors predicting overall sleep quality score in ACTIVE Dialysis cohort

Result of GEE model; dependent variable sleep quality score, also adjusted for study visit. Negative estimates indicate worse sleep score.

Factor	Estimate (95% CI)	p-value
Total dialysis hour per week	0.02 (-0.02, 0.06)	0.36
Age	-0.02 (-0.04, 0.00)	0.10
Gender (ref=Male)		
Female	-0.65 (-1.24, -0.06)	0.03
Time on dialysis (ref=over 6 months)		
<=6 months	0.41 (-0.44, 1.26)	0.34
Dialysis location (ref=Institution)		
At home	0.00 (-0.76, 0.77)	0.99
Smoking status (ref=Never smoked)		
Past smoker	-0.47 (-1.15, 0.21)	0.18
Current smoker	-0.70 (-1.37, -0.02)	0.04
Number of comorbidities (0-6)	-0.25 (-0.55, 0.06)	0.11
BMI	-0.01 (-0.07, 0.04)	0.60
EQ5D	2.97 (1.68, 4.25)	<0.001
History of diabetes	0.64 (-0.14, 1.42)	0.11

Table 3: Association of overall sleep quality score with quality of life measures

GEE model; dependent variable sleep quality score; independent variables QOL measure, time and treatment allocation. Note the estimated magnitudes of the relationship between QOL and overall sleep quality score cannot be compared between EQ5D and PCS/MCS due to the different scales used for each instrument.

QOL measure	Estimate (95% CI)	p-value
EQ5D	1.76 (1.03, 2.48)	<0.01
SF36 MCS	0.05 (0.04, 0.07)	<0.01
SF36 PCS	0.05 (0.03, 0.07)	<0.01