RESEARCH ARTICLE

Effect of Nocturnal Hemodialysis versus Conventional Hemodialysis on End-Stage Renal Disease: A Meta-Analysis and Systematic Review

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Abstract

Objectives

The purpose of this study is to assess the efficacy and safety of nocturnal hemodialysis on end-stage renal disease (ESRD) patients.

Methods

We searched Medline, EmBase, and the Cochrance Central Register of Controlled Trials for studies up to January 2016. Analysis was done to compare variant outcomes of different hemodialysis schedules, including mortality, cardiovascular-associated variables, uremia-associated variables, quality of life (QOL), side-effects, and drug usage.

Results

We collected and analyzed the results of 28 studies involving 22,508 patients in our meta-analysis. The mortality results in this meta-analysis indicated that the nocturnal hemodialysis (NHD) group was not significantly different from conventional hemodialysis (CHD) group (Mortality: OR: 0.75; 95% confidence intervals (CIs): 0.52 to 1.10; p = 0.145), but the CHD group had significantly fewer number of hospitalizations than the NHD group (OR: 1.54; 95%CI: 1.32 to 1.79; p<0.001). NHD was superior to CHD for cardiovascular-associated (left ventricular hypertrophy [LVH]: SMD: -0.39; 95%CI: -0.68 to -0.10; p = 0.009, left ventricular hypertrophy index [LVHI]: SMD: -0.64; 95%CI: -0.83 to -0.46; p<0.001) and uremia-associated intervention results (Serum albumin: SMD: 0.89; 95%CI: 0.41 to 1.36; p<0.001).

For the assessment of quality of life, NHD treatment significantly improved the patients’ QOL only for SF36-Physical Components Summary (SMD: 0.43; 95%CI: 0.26 to 0.60; p<0.001). NHD intervention was relatively better than CHD for anti-hypertensive drug usage.
of Shenyang of China (Grant No. F16-206-9-04), the Key Social Development Program of Science and Technology Commission of Liaoning Province of China (Grant No. 201404046). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

(SMD: -0.48; 95%CI: -0.91 to -0.05; p = 0.005), and there was no difference between groups in our side-effects assessment.

Conclusion
NHD and CHD performed similarly in terms of ESRD patients’ mortality and side-effects. NHD was superior to CHD for cardiovascular-associated and uremia-associated results, QOL, and drug usage; for number of hospitalizations, CHD was relatively better than NHD.

Introduction
End-stage renal disease (ESRD) is a chronic and progressive decline in kidney function, which will eventually lead to uremia and death if it is not treated properly [1]. However, with a progress of technology in past decades, the mortality have not improved significantly and exceeding 20% in chronic hemodialysis patients [2, 3]. Cardiovascular events are the main driving force for this high mortality. Therefore, there is a need for new methods to improve ESRD patients’ cardiovascular and mortality risk.

There are currently two main methods for treatment of ESRD patients. The first, renal transplantation, is a permanent method to cure ESRD patients, however, that means ESRD patients have an issue of having a proper kidney source, thus it has limited application [4, 5]. The second, hemodialysis, is applied worldwide but has a high risk of cardiovascular complications and significantly reduces the quality of life of patients [6, 7]. Nocturnal hemodialysis (NHD) is an important branch of hemodialysis [8, 9]. The schedule for nocturnal dialysis is 3–7 times per week, 7–8 hours every time. This approach extends the effective duration of dialysis without affecting the patient’s daytime activities making it more convenient as a method of treatment. This approach has been widely used in Canada; however, the clinical results still require further examination. Dialysis-related disease is defined as the complications caused by long-term dialysis on ESRD patients; cardiovascular disease is the leading cause of death for ESRD patients [10–13].

Previously, several systemic reviews analyzed the mortality, blood pressure, and urinary-related indexes of NHD for ESRD patients [14–16]. However, the qualities of included studies were relatively low and not comprehensive evaluated all relevant clinical outcomes. Our research is up to date with recently published research and analyzes the effects of NHD by mortality, cardiovascular-related variables, uremia-related variables, quality of life, side-effects, and drug usage to provide better insight in clinical choices for dialysis methods.

Methods
Search strategy and selection criteria
This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement [17] issued in 2009. Any studies that examined NHD versus conventional hemodialysis (CHD) on ESRD patients were eligible for inclusion in our study with no restrictions placed on language or publication status (published, or in press). We searched the Medline, EmBase, and Cochrane Library electronic databases for articles published through January 2016 and used “nocturnal”, “dialysis”, “hemodialysis”, and “controlled trials” as the search keywords. We also conducted manual searches of reference lists from all relevant original articles and reviews to identify additional eligible studies.
A literature search was undertaken independently by 2 authors and any inconsistencies were settled via group discussion. A study was eligible for inclusion if the following criteria were met: (1) the trial investigated nocturnal hemodialysis NHD versus conventional hemodialysis CHD; (2) all of patients included with ESRD; and (3) the outcomes variable included one of the following: mortality, cardiovascular-associated variables, uremia-associated variables, quality of life, side-effect, and drug usage. Case series, reviews, and editorials were excluded.

Data collection and quality assessment

Two reviewers independently extracted all data with disagreements resolved in consultation with third-party investigators. The following items were extracted from the included articles: first author, publication year, country, location or data source, study design, sample size, disease status, mean age, gender proportion, mean duration of dialysis, Dialysis session, and reported outcomes. The outcome assessments included: mortality, cardiovascular-associated variables, uremia-associated variables, quality of life, side-effects, and drug usage. In analysis, the numerical changes between, before, and after dialysis of statistical indicators had priority to be adopted, if not, the dialysis numerical indicators after dialysis was adopted. In addition, the numerical units were adjusted for consistency, such as g/L and g/dL. Two reviewers independently assessed the quality of included studies according to the Cochrane risk of bias tool in the following six domains: selection, performance, detection, attrition, reporting and other bias [18].

Statistical analysis

For our meta-analysis, we used the inverse variance method to pool continuous data and the Mantel-Haenszel method for dichotomous data; the results are presented as standardized mean difference (SMD) with 95% confidence intervals (CIs) and odds ratio (OR) with 95% CIs. The I² statistic was calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. In the absence of statistical heterogeneity (I²≤50%), we used a fixed-effect model, otherwise we used a random-effect model for traditional meta-analysis [19]. To investigate the sources of heterogeneity, predefined subgroup analysis were performed: dialysis schedule and design bias. We assessed for publication bias using the Begg-Mazumdar [20] and Egger’s test [21]. A non-parametric “Trim and Fill” method of assessing publication bias was applied if needed [22]. All tests were two tailed, and a p value of less than 0.05 was deemed statistically significant. We analyzed the data using Review Manager (Version 5.3) and STATA (Version 12.0).

Results

Our research returned 201 results after removing duplicates, from which we collected 28 trials in our meta-analysis (Fig 1). After a full text review, the reasons for exclusion of literature included non-controlled trials, other intervention interference, other similar diseases, and lack of desired outcome assessments. The general characteristics of the included studies are presented in Table 1. In this research, included studies were mainly published in Canada, China, the United States, the United Kingdom, Australia, and Turkey. The study design included eight randomized controlled trials (RCTs) [23–30], seven quasi-RCT [31–37], and thirteen observational studies [38–50].

A total number of 22,508 ESRD patients were examined. The average reported age of patients was between 40–60 years while two studies did not mention the patients’ ages [31, 32]. The number of men was slightly greater than the number of women. The follow-up time
duration was 6 months to 36 months. The schedule for NHD was 3 nights/week or 6–7 nights/week, and 3 times/week for CHD. The summary graph of risk of bias for each study is shown in Fig 2.

In our meta-analysis, mortality results were not significantly different between the NHD group and the CHD group (OR: 0.75; 95%CI: 0.52 to 1.10; p = 0.145). For number of hospitalizations, the CHD group had significantly fewer than NHD group (OR: 1.54; 95%CI: 1.32 to 1.79; p<0.001); in addition, there was no significant difference between the two groups in the number of infection hospitalizations (OR: 1.60; 95%CI: 0.48 to 5.35; p = 0.445).

Within cardiovascular-related variables, left ventricular hypertrophy (LVH, unit: g) and its index (LVHI, unit: g/m²) results both indicate the NHD group has significantly fewer occurrences than the CHD group (LVH: SMD: -0.39; 95%CI: -0.68 to -0.10; p = 0.009, LVHI: SMD: -0.64; 95%CI: -0.83 to -0.46; p<0.001). For the control of blood pressure, systolic blood pressure results also show the NHD group is significantly better than the CHD group (Random model: SMD: -0.33; 95%CI: -0.49 to -0.18; p<0.001, Fixed model: SMD: -0.17; 95%CI: -0.24 to -0.1; p<0.001). The Diastolic blood pressure index also shows the NHD group is significantly better than the CHD group (Diastolic blood pressure: SMD: -0.032; 95%CI: -0.48 to -0.15; p<0.001, Mean arterial pressure: SMD: -0.69; 95%CI: -1.19 to -0.19; p = 0.007, Pulse pressure: SMD: -0.69; 95%CI: -1.19 to -0.19; p = 0.007). For uremia-related variables, the concentration of serum albumin of the NHD group was significantly greater than the CHD group (SMD: 0.89; 95%CI: 0.41 to 1.36; p<0.001); the concentration of serum hemoglobin of the NHD group was also significantly greater than the CHD group (SMD: 0.42; 95%CI: 0.05 to 0.78; p = 0.025). The urea clearance index in the NHD group was significantly higher than the CHD group (SMD: 2.61; 95%CI: 1.76 to 3.46; p<0.001), and urea reduction ratio was also better in the NHD group (SMD: 1.39; 95%CI: 0.49 to 2.30; p = 0.003).
Table 1. Characters of included studies.

| Author     | Year | Country          | Location or data source                          | Study design          | Sample size (NHD) | Disease status | Mean age (year) | Male (%) | Mean duration of dialysis (mo)* | Dialysis session | Reported outcomes                      |
|------------|------|------------------|-------------------------------------------------|-----------------------|-------------------|----------------|-----------------|----------|-------------------------------|-----------------|----------------------------------------|
| Chan[38]   | 2002 | Canada           | Toronto General Hospital                        | Observation cohort study | 41(28)            | ESRD (end-stage renal disease) | 47 (11) | N/A              | NHD: 3.4Y; CHD: 2.8Y | 8–10hours, every night | 4hours, 3 times/week | LVHI, BP, Hb. |
| Friedman[39]| 2002 | Canada           | Humber River Regional Hospital                  | Cross-sectional cohort study | 54(23)            | ESRD             | 44 (20–65) | 63.0%  | NHD: 100(83) M; CHD: 29(17)M | 6–7nights/week  | 3 times/week | Albumin |
| Heidenheim[31]| 2003 | Canada           | London (Canada) Health Sciences Centre          | Prospective nonrandomized (controlled) study | 45(12)            | ESRD             | N/A            | N/A       | 18M                      | 6 nights/week  | 3 times/week | QOL; |
| Nesrallah[32]| 2003 | Canada           | London (Canada) Health Sciences Centre          | Prospective nonrandomized (controlled) study | 43(12)            | ESRD             | N/A            | N/A       | 18M                      | 6 nights/week  | 3 times/week | BP; Drug usage |
| Pierratos[40]| 2004 | Canada           | Humber River Regional Hospital                  | Retrospective study     | 88                | ESRD             | 49 (11)       | 65.0%   | 30(27)M                    | 3–4nights/week | - | QOL; LVH; |
| Lindsay[33]| 2004 | Canada           | London (Canada) Health Sciences Centre          | Prospective controlled study | 45(12)            | ESRD             | 46.7 (10.5) (28–76) | 67.0%     | 5–36M                    | 5–6 nights/week | 3 times/week | BP; Mortality; |
| Schwartz[41]| 2005 | Canada           | Humber River Regional Hospital                  | Retrospective cohort study | 95(63)            | ESRD             | 49.7 (5.7)    | 68.0%   | 12M                      | 5–6 nights/week | 3 times/week | Hb; Drug usage |
| Culleton[23]| 2007 | Canada           | University of Calgary and University of Alberta | Randomized Controlled study | 52(26)            | ESRD             | 54.1 (12.8)   | 62.7%   | 6M                       | 6 nights/week  | 3 times/week | LVH; QOL; BP; Drug usage |
| Johansen[42]| 2009 | U.S              | United States Renal Data System database        | Observation cohort study | 1034 (94)        | ESRD             | 46.7 (17.4)  | 65.9%   | 36M                      | 5–6 nights/week | 3 times/week | Mortality; Hospitalization |
| Manns[24]  | 2009 | Canada           | University of Calgary and University of Alberta | Randomized Controlled study | 51(26)            | ESRD             | 54.1 (12.8)   | 62.7%   | 6M                       | 5–6 nights/week | 3 times/week | QOL |
| Powell[43] | 2009 | U.K              | Western Infirmary renal unit                    | Case-Controlled study   | 106(53)           | ESRD             | 51.2 (15.5)   | 74.5%   | >12M                     | 3 times/week  | 3 times/week | URR; HB; BP; Drug usage |
| van Eps[44]| 2010 | Australia        | Princess Alexandra Hospital                    | Observation cohort study | 235(63)           | ESRD             | 56.5 (15.1)   | 63.8%   | 12M                      | 3.5–4 times/week | 3 times/week | Side-effects; Mortality |
| Lacson[45] | 2010 | U.S              | Fresenius Medical Care, North America           | Case-Controlled study   | 15989 (655)      | ESRD             | 61.9 (15)     | 53.6%   | 12M                      | 3 times/week  | 3 times/week | Mortality; Hospitalization; QOL; BP |

(Continued)
Table 1. (Continued)

| Author         | Year | Country          | Location or data source                      | Study design             | Sample size (NHD) | Disease status | Mean age (year) | Male (%) | Mean duration of dialysis (mo)* | Dialysis session NHD | CHD | Reported outcomes |
|----------------|------|------------------|----------------------------------------------|--------------------------|-------------------|----------------|----------------|----------|--------------------------------|----------------------|-----|------------------|
| Walsh[25]      | 2010 | Canada           | University of Calgary and University of Alberta | Randomized Controlled study | 51(26)            | ESRD           | 54.1 (12.8) | 62.7%    | 6M                             | 5–6 nights/week       |     | Albumin;         |
| Jin[34]        | 2011 | China            | Second Military Medical University Changzheng Hospital | Nonrandomized control study | 90(32)            | ESRD           | 45 (10.8)    | 91.0%    | 12M                            | 3 nights/week         |     | BP; LVHI;         |
| Rocco[26]      | 2011 | U.S              | Frequent Hemodialysis Network (FHN) Trial Group | Randomized Controlled study | 87(45)            | ESRD           | 52.8 (13.6) | 65.5%    | 12M                            | 6 nights/week         |     | Mortality; LVH; |
| Ok[35]         | 2011 | Turkey           | Long Dialysis Study Group                    | Prospective controlled study | 494 (247)        | ESRD           | 45.5 (13.4) | 68.1%    | 12M                            | 3 nights/week         |     | BP; Hospitalization; |
| Overgaard[46]  | 2011 | Canada           | Toronto, Ontario                            | Retrospective study       | 19(8)             | N/A            | 52 (27–68)  | N/A      | 31M                            | 6 nights/week         |     | BP               |
| Rocco[27]      | 2011 | U.S              | Frequent Hemodialysis Network (FHN) Trial Group | Two separate randomized study | 332(87)          | ESRD           | 50.4 (13.9) | 62.0%    | 12M                            | 6 nights/week         |     | Mortality; LVH; |
| Chan[28]       | 2012 | Canada           | Frequent Hemodialysis Network (FHN) Trial Group | Randomized Controlled study | 87(45)            | ESRD           | 52.8 (13.6) | 65.5%    | 12M                            | 6 nights/week         |     | LVM;             |
| Demirci[36]    | 2012 | Turkey           | Long Dialysis Study Group                    | Prospective controlled study | 120(60)          | ESRD           | 49 (11)     | 69.2%    | 12M                            | 3 nights/week         |     | BP; LVH;         |
| Jin[37]        | 2012 | China            | Second Military Medical University Changzheng Hospital | Nonrandomized control study | 90(32)           | ESRD           | 45 (10.8)   | 91.0%    | 12M                            | 3 nights/week         |     | BP; Hemoglobin; |
| Lacson[47]     | 2012 | Canada           | Fresenius Medical Care, North America        | Observation cohort study  | 2808 (746)       | ESRD           | 53.8 (14.2) | 66.3%    | 24M                            | 3 times/week          |     | Mortality; PB; |
| Chan[29]       | 2013 | Canada           | Frequent Hemodialysis Network (FHN) Trial Group | Randomized Controlled study | 87(45)           | ESRD           | 52.8 (13.7) | 65.5%    | 12M                            | 6 nights/week         |     | LVM;             |
| Demirci[48]    | 2013 | Turkey           | Long Dialysis Study Group                    | Prospective cohort study  | 112(57)          | ESRD           | 48 (11.8)   | 70.5%    | 12M                            | 3 nights/week         |     | BP; Albumin; Hemoglobin; |
| Overgaard[49]  | 2013 | Canada           | Toronto, Ontario                            | Retrospective study       | 12(6)            | N/A            | 51 (27–66)  | N/A      | 31M                            | 6 nights/week         |     | -                |

(Continued)
For the assessment of quality of life (QOL), NHD treatment only had significantly improved results for the patient in the SF36-Physical Components Summary (SMD: 0.43; 95% CI: 0.26 to 0.60; p < 0.001). The results of the European QOL (SMD: -0.34; 95%CI: -1.83 to 1.14; p = 0.651) and the SF36-Mental Components Summary (SMD: 0.11; 95%CI: -0.07 to 0.28; p = 0.226) showed no significant difference between groups. In the patients’ drug usage assessment, the anti-hypertensive drug dosage in the NHD group was significantly lower than in the CHD group after dialysis (SMD: -0.48; 95%CI: -0.91 to -0.05; p = 0.005). However, the dosage of EPO was not different between groups (SMD: -0.23; 95%CI: -0.60 to 0.14; p = 0.222).

In our assessment of the side effects of dialysis, the bacteremia (OR: 1.89; 95%CI: 0.96 to 3.74; p = 0.067) and septic (OR: 2.58; 95%CI: 0.73 to 9.16; p = 0.141) both showed no difference between groups.

Performing subgroup analysis, it was found that treatment with nocturnal dialysis 3 times/week yielded a significantly lower mortality rate than the control group (OR: 0.56; 95%CI: 0.34 to 0.92; p = 0.021; I² = 74.8%), while the use of dialysis >3times/week yielded no significant differences (OR: 1.47; 95%CI: 0.68 to 3.19; p = 0.334; I² = 30.6%). Through subgroup analysis of study designs it was discovered that randomized controlled trials and non-randomized controlled trials showed no significant differences in results (RCTs: OR: 0.98; 95%CI: 0.29 to 3.34; p = 0.977; Non-RCTs: OR: 0.73; 95%CI: 0.48 to 1.11; p = 0.140) (Table 2). Only in non-RCT researches, haemoglobin concentration showed significant difference between nocturnal dialysis and control group (SMD: 0.49; 95%CI: 0.10 to 0.88; p = 0.013). In the drug usage assessment, anti-hypertensive drug dosage in patients received more than 3 times per week nocturnal hemodialysis subgroup was significant less than CHD group (SMD: -0.64; 95%CI: -0.92 to -0.37; p<0.001), and in RCT design studies the anti-hypertensive drug dosage in the NHD group was significantly lower than in the CHD group (SMD: -0.64; 95%CI: -0.92 to -0.37; p<0.001). In subgroup analysis, the EPO dosage of 3 times/week subgroup showed significant less than CHD group (SMD: -0.45; 95%CI: -0.83 to -0.06; p = 0.022). However, the heterogeneity was not obviously reduced in all subgroup analysis.

There was publication bias was found in systolic blood pressure results (Table 3, Begg’s test, p = 0.592; Egger’s test, p = 0.001). However, no other publication bias was found. After correction of the results with ”Trim and Fill” method the conclusion was not changed.
Fig 2. Methodological quality of trials included in the meta-analysis. Risk of bias graph and summary.

doi:10.1371/journal.pone.0169203.g002
Discussions

In this review, we analyzed the effects of NHD versus CHD in the treatment of ESRD. Our analysis included 28 trials with 22,508 patients. Our results demonstrate that NHD and CHD are similar in mortality and side-effects, and that NHD is superior to CHD in cardiovascular-associated and uremia-associated markers and in QOL and drug usage. CHD is relatively better than NHD for number of hospitalizations. In general, NHD has more advantages in clinical applications for ESRD patients.

In previously published meta-analyses, the results assessment was not comprehensive. Hui MJ et al. studied the effects of long-time dialysis in daytime or nighttime on survival rate compared to that of conventional hemodialysis [16]. Results showed that the survival rate of patients using prolonged hemodialysis was significant higher than those using conventional hemodialysis; however, residual confounders, which include the patients’ age, sex, presence of diabetes, and catheter use, interferes with the results in observational studies. This study included literatures with lower design quality while not having a comprehensive assessment index. Our research included more high quality design articles to find that nocturnal dialysis does not significant improve the mortality of patients; however, subgroup analysis of treatment 3times/week showed reduced mortality rates. This may be due to the fact that the study used patients with relatively mild uremic symptoms while further study is needed to draw conclusions for the

Table 2. Subgroup analysis of nocturnal and conventional hemodialysis on ESRD patients.

| Outcome               | Subgroup        | No. of trials | OR/SMD | LCI   | UCI   | p value | Heterogeneity | p for Heterogeneity |
|-----------------------|-----------------|---------------|--------|-------|-------|---------|---------------|---------------------|
| Mortality             | >3 night/week   | 5             | 1.47   | 0.68  | 3.19  | 0.334   | 30.60%        | 0.217               |
|                       | 3 night/week    | 6             | 0.56   | 0.34  | 0.92  | 0.021   | 74.80%        | 0.001               |
|                       | Randomized design | 3           | 0.98   | 0.29  | 3.34  | 0.977   | 0%            | 0.552               |
|                       | Nonrandomized design | 8          | 0.73   | 0.48  | 1.11  | 0.14    | 73.10%        | 0.001               |
| Systolic blood pressure | >3 night/week | 4             | -0.48  | -0.71 | -0.25 | <0.001  | 0%            | 0.911               |
|                       | 3 night/week    | 6             | -0.27  | -0.44 | -0.09 | 0.003   | 47.20%        | 0.092               |
|                       | Randomized design | 3           | -0.47  | -0.71 | -0.22 | <0.001  | 0%            | 0.086               |
|                       | Nonrandomized design | 7          | -0.29  | -0.46 | -0.11 | 0.001   | 45.90%        | 0.803               |
| Albumin               | >3 night/week   | 1             | 7.26   | 5.77  | 8.76  | <0.001  | -             | -                   |
|                       | 3 night/week    | 5             | 0.4    | 0.21  | 0.59  | <0.001  | 67.70%        | 0.015               |
| Haemoglobin           | >3 night/week   | 3             | 1.2    | -1.38 | 3.77  | 0.363   | 98%           | <0.001              |
|                       | 3 night/week    | 7             | 0.17   | -0.013 | 0.36 | 0.068   | 70%           | 0.003               |
|                       | Randomized design | 1           | -0.3   | -0.85 | 0.26  | 0.293   | -             | -                   |
|                       | Nonrandomized design | 9          | 0.49   | 0.1   | 0.88  | 0.013   | 94%           | <0.001              |
| Urea clearance index  | >3 night/week   | 2             | 7.12   | -1.97 | 16.21 | 0.125   | 97.20%        | <0.001              |
|                       | 3 night/week    | 3             | 1.83   | 1.05  | 2.61  | <0.001  | 93.90%        | <0.001              |
| Anti-blood pressure drug | >3 night/week | 2             | -0.64  | -0.92 | -0.37 | <0.001  | 0%            | 0.807               |
|                       | 3 night/week    | 2             | -0.32  | -1.23 | 0.6   | 0.498   | 88.10%        | 0.004               |
|                       | Randomized design | 2           | -0.64  | -0.92 | -0.37 | <0.001  | 0%            | 0.807               |
|                       | Nonrandomized design | 2          | -0.32  | -1.23 | 0.6   | 0.498   | 88.10%        | 0.004               |
| EPO usage             | >3 night/week   | 4             | 0      | -0.75 | 0.75  | 0.994   | 86.30%        | <0.001              |
|                       | 3 night/week    | 3             | -0.45  | -0.83 | -0.06 | 0.022   | 74.80%        | 0.019               |
|                       | Randomized design | 1           | 0.18   | -0.27 | 0.63  | 0.434   | -             | -                   |
|                       | Nonrandomized design | 6          | -0.3   | -0.7  | 0.09  | 0.132   | 81.50%        | <0.001              |

Abbreviations: ESRD: End-stage Renal Disease; OR: Odds ratio; SMD: Standard Mean Difference; LCI: Lower Confidence interval; UCI: Upper Confidence interval.

doi:10.1371/journal.pone.0169203.t002
Table 3. Results of treatment effects of NHD versus CHD on end-stage renal failure patients.

| Outcomes                      | No. of trials | Effect size | Value  | LCI   | UCI   | P value | Heterogeneity | P for Heterogeneity | Model | Begg’s test | Egger’s test | Favors |
|-------------------------------|---------------|-------------|--------|-------|-------|---------|---------------|----------------------|-------|-------------|-------------|--------|
| Mortality                     |               |             |        |       |       |         |               |                      |       |             |             |        |
| Mortality                     | 11            | OR          | 0.75   | 0.52  | 1.1   | 0.145   | 63.40%         | 0.002                | Random | 0.533       | 0.87        | Equal  |
| Hospitalization               |               |             |        |       |       |         |               |                      |       |             |             |        |
| Number of Hospitalization     | 2             | OR          | 1.54   | 1.32  | 1.79  | <0.001  | 0%            | 0.549                | Fixed  | -           | -           | CHD group |
| Number of Infection hospitalization | 1           | OR          | 1.6    | 0.48  | 5.35  | 0.445   | -             | -                    | -      | -           | -           | Equal  |
| Cardiovascular-associated variables |             |             |        |       |       |         |               |                      |       |             |             |        |
| Left ventricular hypertrophy (g) | 3             | SMD         | -0.39  | -0.68 | -0.1  | 0.009   | 0%            | 0.74                 | Fixed  | 1           | 0.874       | NHD group |
| Left ventricular hypertrophy index(g/m2) | 5             | SMD         | -0.64  | -0.83 | -0.46 | <0.001  | 0%            | 0.837                | Fixed  | 0.806       | 0.669       | NHD group |
| Systolic blood pressure       | 10            | SMD         | -0.33  | -0.49 | -0.18 | <0.001  | 48.50%        | 0.042                | Random | 0.592       | 0.001       | NHD group |
| Diastolic blood pressure      | 7             | SMD         | -0.32  | -0.48 | -0.15 | <0.001  | 0%            | 0.967                | Fixed  | 0.368       | 0.295       | NHD group |
| Mean arterial pressure        | 2             | SMD         | -0.69  | -1.19 | -0.19 | 0.007   | 0%            | 0.646                | Fixed  | -           | -           | NHD group |
| Pluse pressure                | 2             | SMD         | -0.43  | -0.75 | -0.12 | 0.007   | 0%            | 0.326                | Fixed  | -           | -           | NHD group |
| Uremia-associated variables   |               |             |        |       |       |         |               |                      |       |             |             |        |
| Albumin                       | 6             | SMD         | 0.89   | 0.41  | 1.36  | <0.001  | 94.70%        | <0.001               | Random | 0.133       | 0.186       | NHD group |
| Haemoglobin                   | 10            | SMD         | 0.42   | 0.05  | 0.78  | 0.025   | 93.40%        | <0.001               | Random | 0.721       | 0.248       | NHD group |
| Urea clearance index          | 5             | SMD         | 2.61   | 1.76  | 3.46  | <0.001  | 94.60%        | <0.001               | Random | 0.462       | 0.757       | NHD group |
| Urea Reduction ratio(%)       | 3             | SMD         | 1.39   | 0.49  | 2.3   | 0.003   | 91.60%        | <0.001               | Random | 1           | 0.698       | NHD group |
| QOL                           |               |             |        |       |       |         |               |                      |       |             |             |        |
| European Quality of life      | 2             | SMD         | -0.34  | -1.83 | 1.14  | 0.651   | 92.30%        | <0.001               | Random | -           | -           | Equal  |
| SF36(Mental Components Summary) | 2             | SMD         | 0.11   | -0.07 | 0.28  | 0%      | 0.605         | Fixed                | -      | -           | -           | Equal  |
| SF36(Physical Components Summary) | 2             | SMD         | 0.429  | 0.258 | 0.6   | <0.001  | 32.50%        | 0.224                | Fixed  | -           | -           | NHD group |
| Drug usage                    |               |             |        |       |       |         |               |                      |       |             |             |        |
| Anti-blood pressure drug      | 4             | SMD         | -0.48  | -0.91 | -0.05 | 0.03    | 76.60%        | 0.005                | Random | 0.734       | 0.585       | NHD group |
| EPO usage                     | 7             | SMD         | -0.23  | -0.6  | 0.14  | 0.222   | 82.20%        | <0.001               | Random | 0.23        | 0.302       | Equal  |
| Side Effect                   |               |             |        |       |       |         |               |                      |       |             |             |        |
| Bacteremia                    | 2             | OR          | 1.89   | 0.96  | 3.74  | 0.067   | 4.10%         | 0.307                | Fixed  | -           | -           | Equal  |
| Septic                        | 2             | OR          | 2.58   | 0.73  | 9.16  | 0.141   | 85.80%        | 0.008                | Random | -           | -           | Equal  |

Abbreviation: SMD: Standardized Mean Difference; OR: odds ratio; LCI: Lower confidence interval; UCI: Upper confidence interval; NHD: Nocturnal Hemodialysis; CHD: Conventional Hemodialysis

doi:10.1371/journal.pone.0169203.t003
Specific causes. Julia Thumfart et al. evaluated the effect of intensified nocturnal hemodialysis on ESRD patients compared to conventional hemodialysis in 2014 [15]. That study found that intensified hemodialysis could significantly improve the patients’ blood pressure, uremia-associated variables, and psychosocial variables, and could reduce the usage of antihypertensive and phosphate binders. However, there was no assessment of patients’ mortality and QOL. Our research supports the evidence that intensified hemodialysis could improve cardiovascular-related and uremia-related indicators; we also defined that nocturnal dialysis could improve the patients’ QOL. Paweena Susantitaphong et al. assessed the effects of frequent nocturnal hemodialysis on ESRD patients using the indicators of left ventricular mass and cardiovascular mortality in 2012 [14]. Unfortunately, this research had a paucity of randomized controlled trials. The results supported that frequent or extend hemodialysis could improve cardiac morphology and function; however the outcome of long-term clinical application was limited. Our study includes a longer follow-up period of up to 36 months and RCTs. Our results support the above conclusion and consider long-time nocturnal hemodialysis as beneficial for cardiovascular and uremia-related indicators.

It is very common for cardiovascular complications to occur in long-term hemodialysis patients, including hypertension, coronary heart disease, arrhythmia, and heart failure. Cardiac vascular disease events like cerebrovascular accident, ischemic heart disease, congestive cardiac failure, peripheral vascular disease are also much more prevalent in the chronic kidney disease population. Furthermore, cardiovascular complications are the most common causes of death in ESRD patients and the mortality rate for dialysis patients is up to 10–30 times higher than the matched population [51]. The high mortality indicates the effect of drugs to reduce the incident of cardiovascular disease is not ideal. Therefore, researchers presume the incidence of cardiovascular disease in dialysis patients may have a special pathophysiological process.

There are two parallel factors which may contribute to cardiovascular disease in ESRD patients. The first is a change of cardiac morphological including LVH and left ventricular (LV) dysfunction caused by mechanical or hemodynamic overload and the second being the change of vasculature including atherosclerosis and vascular calcification. These two factors can eventually result in cardiomyopathy and arterial thrombosis [52]. Uremia-related hyperphosphatemia, high calcium and phosphorus deposition, and hyperparathyroidism may be the direct reason for vascular calcification in ESRD patients. Currently it is popular to assess the patient’s dialysis schedule with cardiovascular-related symptoms, in which left ventricular hypertrophy is an important predictor of cardiovascular side effects. Thus, many RCTs use left ventricular mass (LVM) as the primary outcome [23, 28]. Our results show nocturnal dialysis have positive effects on the prevention of cardiovascular disease, which can enhance blood pressure control and reduce serum phosphate, hence reducing the risk of cardiovascular disease.

Although our study shows nocturnal dialysis has a great positive effect on ESRD patients, this approach also has a higher failure rate. For example, a 12 month follow-up period study pointed out that the technique’s survival rate is 79.2% [45]; a 24 months follow-up period study showed the technique’s survival rate by then was only 24.93% [47], meaning about 3/4 of ESRD patients were unable to continue nocturnal hemodialysis treatment. These studies found that the reasons of technique failure included infection, catheter dysfunction, and psychosocial problems in the early stage and ultrafiltration-failure and catheter-related infection in later stages. Therefore further research is needed to look into ways of increasing the technique’s survival rate on patients with high frequency nocturnal dialysis by improving technology and reducing complications.

We comprehensively evaluated the outcome measurements of nocturnal dialysis for ESRD, but still our study had several limitations. First, we did not have specific individual data for all
the trials and thus our statistical approach was done at a study level. Second, the quality of included trials was relatively low, although this review included many outcome measures, single measure conclusions were considered from small sample studies of low quality. Third, there was heterogeneity in several outcomes among included trials. Finally, we were not able to use subgroup analysis or meta-regression to reduce the heterogeneity because there was a lack of trials using a single medicine.

Nocturnal hemodialysis and conventional hemodialysis perform similarly in ESRD patients' mortality and side-effects. In cardiovascular-associated and uremia-associated results NHD is superior to CHD; and in QOL and drug usage NHD intervention is relatively better than CHD. For number of hospitalizations, CHD was relatively better than NHD. In general, NHD has more advantages in clinical application for ESRD patients.

**Supporting Information**

S1 Search Strategy. (DOCX)

**Author Contributions**

Conceived and designed the experiments: FL YS LY.

Performed the experiments: FL YS TX LS LL WS XF JM LW.

Analyzed the data: FL YS TX LS LL WS XF JM LW.

Contributed reagents/materials/analysis tools: LY.

Wrote the paper: FL YS.

**References**

1. O’Lone E, Connors M, Masson P, Wu S, Kelly PJ, Gillespie D, et al. Cognition in People With End-Stage Kidney Disease Treated With Hemodialysis: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2016.

2. Kramann R, Floege J, Ketteler M, Marx N, Brandenburg VM. Medical options to fight mortality in end-stage renal disease: a review of the literature. Nephrol Dial Transplant. 2012; 27(12):4298–4307. doi: 10.1093/ndt/gfs400 PMID: 23045427

3. Stenvinkel P. Inflammation in end-stage renal disease: the hidden enemy. Nephrology (Carlton). 2006; 11(1):36–41.

4. Salari A, Monfared A, Fahim SH, Khosravi M, Lebadi M, Mokhtari G, et al. The survey of diastolic function changes in end-stage renal disease patients before and 3 and 6 months after kidney transplantation. Transplant Proc. 2012; 44(10):3007–3012. doi: 10.1016/j.transproceed.2012.03.060 PMID: 23195015

5. Niakas D, Kontodimopoulos N. Is renal transplantation the most cost-effective and preferable therapy for patients suffering from end-stage renal disease or not? Health Policy. 2009; 89(3):329–331. doi: 10.1016/j.healthpol.2008.07.005 PMID: 18768237

6. Sawant A, House AA, Overend TJ. Anabolic Effect of Exercise Training in People with End-Stage Renal Disease on Hemodialysis: A Systematic Review with Meta-analysis. Physiotherapy Can. 2014; 66(1):44–53. doi: 10.3138/pjc.2012-59 PMID: 24719508

7. Palamaneer Subash Shantha G, Kumar AA, Sethi M, Khanna RC, Pancholy SB. Efficacy and safety of low molecular weight heparin compared to unfractionated heparin for chronic outpatient hemodialysis in end stage renal disease: systematic review and meta-analysis. PeerJ. 2015; 3:e835. doi: 10.7717/peerj.835 PMID: 25780780

8. Karkar A, Hegbrant J, Strippoli GF. Benefits and implementation of home hemodialysis: A narrative review. Saudi J Kidney Dis Transpl. 2015; 26(6):1095–1107. doi: 10.4103/1319-2442.168556 PMID: 26586045
9. Lewicki MC, Polkinghornere KR, Kerr PG. Debate: Should dialysis at home be mandatory for all suitable ESRD patients?: home-based dialysis therapies are the second choice after transplantation. Semin Dial. 2015; 28(2):147–154. doi: 10.1111/sdi.12322 PMID: 25481976

10. Alkhouli M, Sandhu P, Boobes K, Hatahet K, Raza F, Boobes Y. Cardiac complications of arteriovenous fistulas in patients with end-stage renal disease. Nefrologia. 2015; 35(3):234–245. doi: 10.1016/j.nefro.2015.03.001 PMID: 26299166

11. Silva LS, Oliveira RA, Silva GB, Lima JW, Silva RP, Liborio AB, et al. Cardiovascular disease in patients with end-stage renal disease on hemodialysis in a developing country. Saudi J Kidney Dis Transpl. 2012; 23(2):262–266. PMID: 22382216

12. do Sameiro-Faria M, Kohlova M, Ribeiro S, Rocha-Pereira P, Teixeira L, Nascimento H, et al. Potential cardiovascular risk protection of bilirubin in end-stage renal disease patients under hemodialysis. Biomed Res Int. 2014; 2014:175286. doi: 10.1155/2014/175286 PMID: 25276769

13. Harnett JD, Kent GM, Barre PE, Taylor R, Parfrey PS. Risk factors for the development of left ventricular hypertrophy in a prospectively followed cohort of dialysis patients. J Am Soc Nephrol. 1994; 4(7):1486–1490. PMID: 8161730

14. Susantiphong P, Koulouridis I, Balk EM, Madias NE, Jaber BL. Effect of frequent or extended hemodialysis on cardiovascular parameters: a meta-analysis of studies. Am J Kidney Dis. 2012; 59(5):689–699. doi: 10.1053/j.ajkd.2011.12.020 PMID: 22370022

15. Thumfart J, Pommer W, Querfeld U, Muller D. Intensified hemodialysis in adults, and in children and adolescents. Dtsch Arztebl Int. 2014; 111(14):237–243. doi: 10.3238/arztebl.2014.0237 PMID: 24766711

16. Jin HM, Guo LL, Zhan XL, Pan Y. Effect of prolonged weekly hemodialysis on survival of maintenance hemodialysis patients: a meta-analysis of studies. Nephron Clin Pract. 2013; 123(3–4):220–288. doi: 10.1159/000354709 PMID: 24008276

17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med. 2009; 3(3):e123–130. PMID: 21603045

18. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011; 343:d5928. doi: 10.1136/bmj.d5928 PMID: 22008217

19. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50(4):1088–1101. PMID: 7786990

20. Papageorgiou SN, Dimitraki D, Coolidge T, Kotsanos N. Publication bias & small-study effects in pediatric dentistry meta-analyses. J Evid Based Dent Pract. 2015; 15(1):8–24. doi: 10.1016/j.jebdp.2014.09.001 PMID: 25666576

21. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Stat Med. 2007; 26(25):4544–4562. doi: 10.1002/sim.2889 PMID: 17476644

22. Peters IL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Stat Med. 2007; 26(25):4544–4562. doi: 10.1002/sim.2889 PMID: 17476644

23. Culleton BF, Walsh M, Klarenbach SW, Mortis G, Scott-Douglas N, Quinn RR, et al. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. JAMA. 2007; 298(11):1291–1299. doi: 10.1001/jama.2007.17878421

24. Manns BJ, Walsh MW, Culleton BF, Hemmelgarn B, Tonelli M, Schorr M, et al. Nocturnal hemodialysis does not improve overall measures of quality of life compared to conventional hemodialysis. Kidney Int. 2009; 75(5):542–549. doi: 10.1038/ki.2008.639 PMID: 19109588

25. Walsh M, Manns BJ, Klarenbach S, Tonelli M, Hemmelgarn B, Culleton B. The effects of nocturnal compared with conventional hemodialysis on mineral metabolism: A randomized-controlled trial. Hemodial Int. 2010; 14(2):174–181. doi: 10.1111/j.1542-4758.2009.00418.x PMID: 20041960

26. Rocco MV, Lockridge RS Jr., Beck GJ, Eggers PW, Gassman JJ, Greene T, et al. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. Kidney Int. 2011; 80(10):1080–1091. doi: 10.1038/ki.2011.213 PMID: 21775973

27. Rocco MV, Larive B, Eggers PW, Beck GJ, Chertow GM, Levin NW, et al. Baseline characteristics of participants in the Frequent Hemodialysis Network (FHN) daily and nocturnal trials. Am J Kidney Dis. 2011; 57(1):90–100. doi: 10.1053/ajkd.2010.08.024 PMID: 21122961

28. Chan CT, Greene T, Chertow GM, Kilger AS, Stokes JB, Beck GJ, et al. Determinants of left ventricular mass in patients on hemodialysis: Frequent Hemodialysis Network (FHN) Trials. Circ Cardiovasc Imaging. 2012; 5(2):251–261. doi: 10.1161/CIRCIMAGING.111.969923 PMID: 22360996
29. Chan CT, Greene T, Chertow GM, Kliger AS, Stokes JB, Beck GJ, et al. Effects of frequent hemodialysis on ventricular volumes and left ventricular remodeling. Clin J Am Soc Nephrol. 2013; 8(12):2106–2116. doi: 10.2215/CJN.03280313 PMID: 23970131

30. Kotanko P, Garg AX, Depner T, Pierratos A, Chan CT, Levin NW, et al. Effects of frequent hemodialysis on blood pressure: Results from the randomized frequent hemodialysis network trials. Hemodial Int. 2015; 19(3):386–401. doi: 10.1111/hdi.12255 PMID: 25560227

31. Heidenheimer AP, Muirhead N, Moist L, Lindsay RM. Patient quality of life on quotidian hemodialysis. Am J Kidney Dis. 2003; 42(1 Suppl):36–41. PMID: 12830442

32. Nesrallah G, Suri R, Moist L, Kortas C, Lindsay RM. Volume control and blood pressure management in patients undergoing quotidian hemodialysis. Am J Kidney Dis. 2003; 42(1 Suppl):13–17. PMID: 12830438

33. Lindsay RM, Daily/Nocturnal Dialysis Study G. The London, Ontario, Daily/Nocturnal Hemodialysis Study. Semin Dial. 2004; 17(2):85–91. doi: 10.1111/j.0894-0959.2004.17202.x PMID: 15043607

34. Jin X, Rong S, Mei C, Ye C, Chen J, Chen X. Effects of thrice-weekly in-center nocturnal vs. conventional hemodialysis on endothelial dysfunction. Ther Apher Dial. 2012; 16(4):334–340. doi: 10.1111/j.1744-9987.2012.01070.x PMID: 22817121

35. Demirci MS, Celik G, Ozkahya M, Tumuklu M, Toz H, Asci G, et al. Effects of thrice weekly nocturnal hemodialysis on arterial stiffness. Atherosclerosis. 2012; 220(2):477–485. doi: 10.1016/j.atherosclerosis.2011.11.015 PMID: 22172590

36. Chan CT, Floras JS, Miller JA, Richardson RM, Pierratos A. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. Kidney Int. 2002; 61(6):2235–2239. doi: 10.1046/j.1523-1755.2002.00362.x PMID: 12028465

37. Friedmann AN, Bostom AG, Levey AS, Rosenberg IH, Selhub J, Pierratos A. Plasma total homocysteine levels among patients undergoing nocturnal versus standard hemodialysis. J Am Soc Nephrol. 2002; 13(1):265–268. PMID: 11752047

38. Schwartz DI, Pierratos A, Richardson RM, Fenton SS, Chan CT. Impact of nocturnal home hemodialysis on anemia management in patients with end-stage renal disease. Clin Nephrol. 2005; 63(3):202–208. PMID: 15786821

39. Johansen KL, Zhang R, Huang Y, Chen SC, Blagg CR, Goldfarb-Rumyantsev AS, et al. Survival and hospitalization among patients using nocturnal and short daily compared to conventional hemodialysis: a USRDS study. Kidney Int. 2009; 76(9):984–990. doi: 10.1038/ki.2009.291 PMID: 19692997

40. Powell JR, Oluwaseun O, Woo YM, Padmanabhan N, Narasingh A, Latta C, et al. Ten years experience of in-center thrice weekly long overnight hemodialysis. Clin J Am Soc Nephrol. 2009; 4(6):1097–1101. doi: 10.2215/CJN.06511208 PMID: 19470659

41. Van Eps CL, Jones M, Ng T, Johnson DW, Campbell SB, Isbel NM, et al. The impact of extended-hours home hemodialysis and buttonhole cannulation technique on hospitalization rates for septic events related to dialysis access. Hemodial Int. 2010; 14(4):451–463. doi: 10.1111/j.1542-4758.2010.00463.x PMID: 20955279

42. Lacson E Jr., Wang W, Lester K, Ofsthun N, Lazarus JM, Hakim RM. Outcomes associated with in-center nocturnal hemodialysis from a large multicenter program. Clin J Am Soc Nephrol. 2010; 5(2):220–226. doi: 10.2215/CJN.06700809 PMID: 19965529

43. Overgaard C, Chowdhary S, Zur R, Bui S, Wainstein R, Barolet A, et al. 144 Comparison of coronary vasoreactivity in end-stage renal disease patients receiving conventional intermittent vs. nocturnal hemodialysis. Can J Cardiol. 2011; 27(5):S114.

44. Lacson E Jr., Xu J, Suri RS, Nesrallah G, Lindsay R, Garg AX, et al. Survival with three-times weekly in-center nocturnal versus conventional hemodialysis. J Am Soc Nephrol. 2012; 23(4):687–695. doi: 10.1681/ASN.2011070674 PMID: 22362905

45. Demirci C, Ozkahya M, Demirci MS, Asci G, Kose T, Colak T, et al. Effects of three times weekly eight-hour nocturnal hemodialysis on volume and nutritional status. Am J Nephrol. 2013; 37(6):559–567. doi: 10.1159/000351182 PMID: 23735837
49. Overgaard CB, Chan W, Chowdhary S, Zur RL, Morrison L, Bui S, et al. Nocturnal hemodialysis restores impaired coronary endothelial function in end-stage renal patients receiving conventional hemodialysis. Circulation. 2013; 128(22 Supplement):A17626.

50. Wald R, Goldstein MB, Perl J, Kiaii M, Yuen D, Wald RM, et al. The Association Between Conversion to In-centre Nocturnal Hemodialysis and Left Ventricular Mass Regression in Patients With End-Stage Renal Disease. Can J Cardiol. 2016; 32(3):369–377. doi: 10.1016/j.cjca.2015.07.004 PMID: 26386732

51. Longenecker JC, Coresh J, Powe NR, Levey AS, Fink NE, Martin A, et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. J Am Soc Nephrol. 2002; 13(7):1918–1927. PMID: 12089389

52. Moradi H, Sica DA, Kalantar-Zadeh K. Cardiovascular burden associated with uremic toxins in patients with chronic kidney disease. Am J Nephrol. 2013; 38(2):136–148. doi: 10.1159/000351758 PMID: 23941724