Does dialysis modality affect development of cognitive impairment?

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Word limit: 1440/1500 words max including abstract but excluding references

Abstract (74/75 words maximum)

Denise Neumann and colleagues attempted to investigate whether dialysis modality (peritoneal dialysis compared to hemodialysis) could affect changes in neurocognition. Their study highlights all the challenges around such research. These include using appropriate tests to investigate cognition, challenges of comparing people on different modalities considering that different types of people chose these, and reasons for drop-out that affect assessment of neurocognition during follow-up. More studies in this area are needed to inform patient choice.

Although the incidence of older patients starting dialysis has not changed in the past years, due to demographic change and the ageing population, older people (aged 75+) form a bigger part of the prevalent population on dialysis.[1]
We know that people with CKD have high prevalence of multimorbidity.[2] Compared to the general population of the same age and sex, there appears to be a higher prevalence of cognitive impairment amongst those with reduced eGFR.[3] A recent study indicates that up to 70% of patients on hemodialysis (HD) may be affected.[4]

To date there is little evidence to help patients decide the dialysis modality. Patients may make differing choices if they knew that dialysis affects cognition. Data comparing cognition on different dialysis modalities are needed, and in this issue Neumann et al. have attempted to address this question.[5]

In order to appreciate the challenges of such research it may be useful to contrast the ideal theoretical study design of such a question with the practical challenges that Neumann et al. encountered during their study.

In an ideal study investigating how dialysis modality affects cognition, one would randomise people starting dialysis to either hemodialysis or peritoneal dialysis, quantify cognition before dialysis start at baseline and then several times during follow-up. Early changes in cognition may be due to treating uraemia, therefore, a long-term follow-up of at least a year or even more would be needed. Power calculations would need to be adjusted for the high early mortality in people starting dialysis. In reality to date there has been no trial successful in recruiting sufficient numbers of participants who agree to be randomized to different dialysis modalities, so clearly such a randomized trial is not feasible.

An observational study of this question would need to be ideally as similar as possible to the suggested hypothetical trial. The investigator would attempt to recruit patients starting dialysis, and try to ensure that those on differing modalities are as similar in comorbidity profile and baseline cognition as much as possible. The investigator would then

investigate cognition at follow-up, to see how cognition is affected by dialysis modality, adjusted for confounding factors. As outlined above, such a study would need to take into account the early mortality in dialysis starters, not over-interpret early changes, and therefore require sufficiently long of follow-up of one or more years.

Neumann et al capitalized in their work on an existing German multicenter study of prevalent dialysis patients who were recruited approximately 6-24 months after starting dialysis.[5] Such a design means that those patients who died during the early phases of dialysis are excluded, and that patients are likely to be in steady state. The baseline assessment of these patients took place in May 2014-2015, and follow-up assessment a year later.[5]

Patients who undergo cognitive assessments need to be able to do these assessments. This posed a significant practical challenge:[5]

Of 767 patients who were approached for cognitive assessments as part of the study, 366 patients of whom 304 were on HD had to be excluded at baseline. Visual impairment was the most common reason (48%), lack of motivation was prevalent in 30%, 12% had motor conditions, and 5% were unable to follow the instructions.

Of the 401 patients who then had a baseline assessment of cognitive function, there were further 130 patients who were not followed up at 12 months, 16% of these died (9% on HD, and 7% on peritoneal dialysis (PD)), and 35% were transplanted or switched dialysis modality (4% on HD, and 31% on PD). A quarter of patients had to be excluded during the one year follow-up because they developed visual problems and motor conditions (21% on HD and 4% on PD).

Patients on HD are likely to be visually impaired and have motor conditions, whilst PD patients cannot do PD unless they can operate the dialysis equipment. Patients on PD are also more likely to be transplanted during follow-up, whilst death rates were broadly similar. All in all this shows the challenges of assessing long-term cognitive function in patients on dialysis, which relate to disability and competing risks of death and transplantation.

Neumann et al report data on the cognitive assessment in the 271 patients who had complete baseline and follow-up cognitive assessment data.[5] Cognitive function was assessed by patient reported cognitive function (KDQOL-SF^{tm25} 3-item subscale) and two tests assessing selective attention (d2-R testing) and executive functioning (TMT-B), by appropriately trained staff. A number of sensitivity analyses found no evidence for dialysis features (e.g timing relative to start of haemodialysis) affecting test quality in patients.[5]

The authors wanted to ensure that the patients on HD and PD were comparable in terms of their psychotropic medication, dialysis vintage and comorbidity profile. In view of the small numbers of the sample, they used a technique called propensity score matching to ensure that these features are balanced in both groups at baseline. This resulted in 62 patients on HD and 12 patients on PD being dropped from further analysis as they could not be matched to a comparable patient on the other dialysis modality. This shows that patients on HD and PD when established on their respective modality are quite distinct in their comorbidity profile and that crude comparisons of cognition are not meaningful as they may be due to case-mix as opposed to the effect of the modality itself.

They then carried out a random effects analysis in this matched cohort. This analysis was taking account of the correlation of the two cognitive scores at baseline and follow-up within the same patient. The authors then plotted predicted population mean scores at baseline and follow-up. Overall, using the objective tests (TMT-B and d2-R) all patients tended to perform better at the second measurement when compared to the first, with no evidence that this increase in performance differed between dialysis modalities. It is unlikely that patients remember how to do these tests well over a year, and so this finding may be a true change in functioning. At both time points, after having taken account of baseline differences between these two groups using propensity score matching, those on PD showed marked better performance than those on HD. In contrast self-reported functioning decreased, and those on HD report somewhat better scores than those on PD though overall the difference appears to have less clinical meaning when contrasted with the magnitude of observed differences in the objective cognitive functioning tests. The

self-reported cognitive functioning did not correlate with the objective psychometric tests at all. There may non-differential misclassification of the self-reported questionnaire data.

This descriptive study shows the difficulties in studying cognition in dialysis patients, with a large number of patients unable to undergo psychometric tests over a prolonged period, especially those on HD, and the importance that case-mix plays on any comparison of cognition between dialysis modalities. We can conclude that if a dialysis patient is fit enough to undergo cognitive testing and if such a patient remains fit and survives the following year without developing motor or visual problems, then this patient may have stable or improved cognition on objective testing. Even if we take baseline comorbidity into account, patients who are stable on PD tend to have better cognition than patients on HD with similar comorbidity profile. These findings may be affected by residual confounding, despite the statistical state of the art efforts to control for this. We cannot exclude that the differences observed in this study are due to patients with better cognitive function who feel competent to do PD preferentially chosing PD over HD to maintain a flexible life-style. From this study, we learn that clinicians cannot rely on self-report alone to assess cognitive functioning over time, as what patients report may not relate to the objective measures.

Clearly, more research is needed on cognitive function using patients starting dialysis with a longer follow-up allowing for competing risks of death, transplantation and the development of visual and motor impairment over time. Neumann et al have made a start on this journey and shown that there are a number of practical difficulties associated with this work.

Figure 1. Conceptual diagram of study of Neumann et al.
The association of interest is highlighted with a blue arrow, drop out is captured by the red box and arrows, measured confounders are indicated by the black boxes, unmeasured factors are in the brown box. The confounding pathways which are analytically removed by propensity score matching are signified with crosses.

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