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THE EFFECT OF THE INTERDIALYTIC INTERVAL ON COGNITIVE FUNCTION IN PATIENTS ON HAEMODIALYSIS

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SUMMARY

Background: Cognitive deficits are common among individuals on haemodialysis (HD). The degree of dysfunction may shift over the course of the interdialytic interval.

Objectives: To use ecological momentary assessment (EMA) to examine the relationship between the length of the interdialytic interval and reports of cognitive dysfunction.

Design: A quantitative study whereby each patient's cognitive functioning was measured during both short and long interdialytic intervals.

Participants: Adults maintained on HD (Female n = 15, Male n = 11; M_{Age} = 42.7 ± 15.8 years) were drawn from a standalone HD unit within a large university medical centre.

Measurements: Tests of baseline neurocognitive functioning were undertaken (Mini-Mental Status Examination, Digit Span, California Verbal Learning Test, Benton Visual Retention Test, Trail-Making Test) and smartphone-based electronic diary reports of cognitive impairment were made around six times each day for one week.

Results: Cognitive function and aptitude in this sample, although low, did not reflect clinically-significant impairment, with a mean Mini-Mental Status Exam score of 25.7 ± 3.0. Diary reports of cognitive impairment were also minimal, with an overall mean rating of .22 out of 5. Contrary

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AUTHOR CONTRIBUTIONS

SLH: Principal Project Leader, conceived study, participated in design and coordination, supervised and participated in conduct of interviews, analysed data, prepared and approved the final manuscript. LDJ: Participated in design and coordination, approved data analysis, edited manuscript, read and approved the final manuscript. SEC: Participated in design, read and approved the final manuscript. MVP: Participated in design and coordination, authorised collection of data, edited manuscript, read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

to expectations, cognitive impairment was significantly greater on the one-day interdialytic days than on Day 2 of the two-day interdialytic interval (β = .094, p = .017).

Conclusions: Although cognitive impairment appears to be mild in stable, young patients with end stage renal disease, volumetric disruptions caused by HD may exacerbate such dysfunction.

Keywords

Cognitive functioning; Haemodialysis; Interdialytic interval

INTRODUCTION

Cognitive impairments are frequently observed among individuals undergoing haemodialysis (HD) (Griva *et al.* 2010; Lux *et al.* 2010; Song *et al.* 2011; Zammit *et al.* 2015; Foster *et al.* 2016; O'lone *et al.* 2016; Drew *et al.* 2017; Iyasere *et al.* 2017). Such deficits may take the form of memory and attention impairment, reduced psychomotor speed and accuracy, and reduced mental efficiency (O'lone *et al.* 2016; Drew *et al.* 2017).

LITERATURE REVIEW

Cognitive impairment is a potent predictor of mortality, contributing to a risk of death three times that of individuals without cognitive dysfunction (Griva *et al.* 2010). Additionally, cognitive impairments persist even when patients are well dialysed, indicating that the dialysis process itself may contribute to reductions in cognitive function. While patients on HD may outperform patients with advanced Chronic kidney disease (CKD) (not on dialysis) on measures of cognitive impairment, dialysis does not appear to return patients to their levels of functioning prior to them having CKD (Evans *et al.* 2004). These changes can have significant clinical consequences as even minor cognitive impairments can affect planning, organisation and flexibility, which may in turn negatively impact the management of daily self-care activities, and treatment adherence (Post *et al.* 2010).

Cognitive performance has been shown to be poorer for patients with end-stage kidney disease (ESKD) compared with earlier-stage CKD as well as the general population (Lambert *et al.* 2017). While dialysis initiation has been associated with improvement in cognitive functioning (Evans *et al.* 2004), residual impairments persist even when patients are well dialysed, suggesting there may be aspects of dialysis that contribute to cognitive impairment.

Several studies have identified shifts in the cognitive functioning related to the length of the interdialytic interval (Griva *et al.* 2003, Lux *et al.* 2010; Costa *et al.* 2014). Studies have reported marked improvement in cognitive functioning following a single dialysis session (Cukor *et al.* 2012; Schneider *et al.* 2015), while others have shown significant declines in cognitive performance hours to days following the completion dialysis sessions (Costa *et al.* 2014), or no effect of dialysis on cognitive function (Lux *et al.* 2010). Possible explanations for the inconsistencies observed across studies include the bias inherent in self-report assessments, or when cognitive functioning was measured relative to HD (Madero *et al.* 2008; Murray 2008).

The use of ecological momentary assessment (EMA), in which individuals are prompted to provide ratings of moods, cognitions and activities multiple times over the course of several days, offers a number of methodological advantages in determining relationships between cognitive functioning and HD. The real-time capture of cognitions, behaviours and emotion reduce recall bias inherent to retrospective self-reports. The repeated measurement of relevant factors in individuals' everyday lives also provides assessments across a range of contexts (Shiffman *et al.* 2008). To our knowledge, only two published studies exist that have used EMA methods in the study of patients undergoing HD (Riis *et al.* 2005; Abdel-Kader *et al.* 2014). Though the use of EMA in health-related studies has grown dramatically over the past decade, the use of experience sampling methods to assess ongoing cognitive functioning is still in its infancy (Sliwinski *et al.* 2018).

AIM OF STUDY

The aim of this study was to examine self-reported cognitive performance as a function of the length of the interdialytic interval in adult maintenance HD outpatients using a combination of EMA-derived measures, clinical neurocognitive interviews, as well as standardised instruments. On the basis of an increasing toxicity model of kidney disease, we hypothesised that diary reports of cognitive impairment would become greater as time since participants' last dialysis increased.

METHODS

PARTICIPANTS

Twenty-six (Female n = 15, Male n = 11) English- and/or Spanish-speaking adults maintained on HD (in a stable condition) for a minimum of three months, participated in the study. The mean age of participants was 42.7 years (SD = 15.8 years, Range 18–77). Other demographic characteristics of the sample are provided in Table 1. Patient-reported causes of ESKD included diabetes mellitus and/or hypertension, chronic glomerulonephritis, systemic lupus erythematosus, complications of pregnancy, cystinosisand focal segmental glomerulosclerosis.

Participants reported that they had been on dialysis for an average of 4.1 years (SD = 3.0, Range <1–10 years). Four had previously used peritoneal dialysis (PD). Two had previously had a kidney transplant. All but one subject came for dialysis three times a week; the remaining participant dialysed four times a week. On average, participants dialysed for 3.28 hours (SD = .33 hours; Median = 3 hours and 15 minutes). No patients reported skipping dialysis sessions, but seven participants reported difficulties staying for their entire treatment session; six patients had shortened treatment at least once in the past month. Potassium, phosphorus and intra-dialytic weight-gain (IWG) values were collected from patient medical records over the six month period surrounding the study assessment period. Weight values were reported each time a patient came to clinic for dialysis. On average, patients gained 3.11kg (SD = .90kg) between dialysis sessions. Weight gain following the two-day interdialytic interval (M = 3.76 kg, SD = 1.07 kg) was significantly greater than over the one-day interval (M = 2.79 kg, SD = .85 kg; $t = -77.04$, $p < .0001$). Potassium and phosphorus levels were collected from patients monthly. The mean level of potassium over the period of interest was 1.70 mmol/L (SD = 2.24 mmol/L); 55% of participants had mean potassium levels outside the target range of between 0.64 and 1.28 mmol/L. The mean level of serum phosphorus was 1.70 mmol/L (SD = 0.49 mmol/L); 59% had phosphorus values outside the target range of between 1.13 and 1.62 mmol/L. High interdialytic weight gain and a large proportion of patients with serum mineral levels outside the acceptable range indicate that disease self-management was relatively poor in this sample.

Attrition was considerable in this sample. Seventeen refused enrolment, withdrew, expired or provided insufficient data. The analysed subsample did not differ significantly from the complete sample in terms of age, gender, education level, employment status, marital status or language spoken. However, none of the dropped subjects had private insurance.

PROCEDURES

Following informed consent, participants completed a battery of self-report instruments, a brief survey of sociodemographic information and a clinical neurocognitive interview during the second hour of a scheduled HD session. Following the completion of their psychosocial and neurocognitive assessments, participants were trained to use an electronic diary system and began a week-long monitoring period, covering two short and one long intradialytic interval (IDI). Data were analysed comparing dialysis days to non-dialysis days, with particular focus on the second day of the long IDI.

All study procedures were approved by the University of California, Irvine, Institutional Review Board on 28 September 2012 (HS# 2012–9049).

MEASURES OF COGNITIVE FUNCTIONING

The primary cognitive assessment was the momentary reports of cognitive functioning in the electronic diary. Standard baseline assessments of cognitive functioning included the (a) Mini-Mental Status Examination (Folstein *et al.* 1975); (b) Digit Span task (Wechsler 1981), a test of auditory, verbal working memory; (c) California Verbal Learning Test (Delis *et al.* 1987, 2000), a measure of immediate and delayed recall; (d) Benton Visual Retention Test (Sivan 1991), a measure of visual perception, memory and the ability to recreate viewed images; and (e) Trail-Making Test (Reitan 1958), a task requiring respondents to “connect the dots” between randomly ordered numbers and letters, that were also administered to participants during the orientation and assessment session. These scales are standard, clinical measures of neurocognitive functioning and have been used extensively among patients with chronic kidney diseases *(cf.* O’lone *et al.* 2016).

ECOLOGICAL MOMENTARY ASSESSMENT

Study participants were provided with a smartphone-based electronic diary system. Approximately five times each day, the diary programme signalled participants to provide information related to their location, activities, social context, moods, diet, fluid and medication consumption, social support and cognitive functioning. Cognitive functioning was assessed by using four items inquiring, in the time since their previous diary entry, (1) how much had they reacted slowly to things that were said or done around them; (2) how much they had difficulty concentrating or thinking; (3) whether or not they became confused at all; and (4) whether or not they found it difficult to make decisions. Symptom severity was rated on a 6-point Likert-type scale: “None of the time”, “A little of the time”, “Some of the time”, “A good bit of the time”, “Most of the time” or “All of the time”. These items were based on the cognitive function subscale of the Kidney Disease Quality of Life-Short Form (Hays *et al.* 1994; Hays *et al.* 1997) and the Beck Depression Inventory (Beck *et al.* 1988).

STATISTICAL ANALYSES

Analyses were completed using the SYSTAT 13 (Systat Software, Inc., San Jose, CA, USA) and Stata 11SE (StataCorp, LP, College Station, TX, USA) statistical packages. Random- and fixed-effect regression models, including mixed models and general estimating equations, with data clustered by person, were used to test the hypotheses that cognitive function would decrease as a function of increased time since dialysis.

RESULTS

BASELINE NEUROCOGNITIVE FUNCTION

Cognitive functioning in this young population was generally low, but most patients did not evidence clinically-significant impairment. Six respondents had an MMSE score below 24, and three respondents had dot-tracing time of greater than 78 seconds, reflecting possible mild cognitive impairment (Crum *et al.* 1993). Measures of working memory, delayed recall and visual perception and memory likewise indicated diminished, but not substantial, impairment.

ELECTRONIC DIARY REPORTS OF COGNITIVE FUNCTIONING

Electronic diary reports of cognitive impairment were minimally present in our cohort (Table 2). Higher scores reflect greater cognitive impairment; overall, levels of cognitive impairment were below 1, or between “None of the time” and “A little of the time”. The symptom with the highest level of self-reported cognitive impairment was trouble thinking, with an average rating of 0.36 out of 5, followed by diary ratings of slowed reaction time, confusion and difficulty making decisions. Although participants did indicate some degree of cognitive impairment in their electronic diaries, these reports were not found to be consistently associated with scores on the baseline clinical measures of neurocognitive functioning. Analyses revealed that diary ratings of slower reaction time were associated with poorer working memory ($\beta = -.15$, $p = .004$) and longer dot-tracing times ($\beta = .004$, $p = .023$). Greater diary-rated confusion was found to be related to lower working memory ($\beta = -.07$, $p = .022$) and visual recall scores ($\beta = -.05$, $p = .004$), as well as longer dot tracing times ($\beta = .002$, $p = .005$). No other significant relationships between the baseline measures and diary reports of cognitive function were observed (all ps > .07).

RELATIONSHIPS BETWEEN ELECTRONIC DIARY REPORTS OF COGNITIVE FUNCTIONING AND THE INTERDIALYTIC INTERVAL

Several of the diary-based measures of cognitive functioning were found to differ between dialysis days and the short IDI and the long IDI. Continuous ratings of confusion were greater on dialysis days when compared to non-dialysis days ($\beta = .097$, $p = .005$); however, no corresponding differences were found in reaction time, trouble thinking or decision making (all ps > .19). Improvement in cognitive functioning was observed during the second day of the long IDI, such that continuous diary ratings of reaction time were worse on short IDIs than on day 2 of the long IDI ($\beta = .21$, $p = .005$). Ratings of trouble thinking, confusion and difficulty making decisions did not differ significantly on short IDIs when compared with the long IDI.

DISCUSSION

A growing body of evidence suggests that patients who have ESKD are burdened with reduced cognitive functioning (Zammit *et al.* 2015; O'lone *et al.* 2016). One hypothesis, a toxicity theory of cognitive functioning, purports that increases in fluid volume over time since dialysis lead to subtle shifts in cognitive abilities (Kurella *et al.* 2004; Dogukan *et al.* 2009; Lux *et al.* 2010), or that the build-up of waste products and minerals in the bloodstream over the interdialytic interval leads to confusion and cognitive impairment (Williams *et al.* 2004). Indeed, consistent with this hypothesis, some studies have shown that cognitive function improves shortly following dialysis (Cukor *et al.* 2012; Schneider *et al.* 2015). However, contrary to our initial expectations, diary-derived measures of cognitive functioning were observed to improve as time since dialysis increased, on the two-day compared to the one-day IDI.

The findings observed here are consistent with an osmotic theory of cognitive impairment that predicts cognitive functioning influenced by the dramatic shifts in fluid and solute levels from the pre- to post-dialytic state. In this instance, cognitive functioning might be expected to improve as time since dialysis wears on, and be poorest during and shortly after dialysis. Indeed, two known dialysis-related syndromes—post-dialysis rebound (Tattersall *et al.* 1996a,b) and dialysis disequilibrium (Silver *et al.* 1996; Murray 2008) are associated with cognitive impairment during and shortly after HD treatment. Though it is not entirely clear how exactly the dialysis procedure contributes to these neurocognitive symptoms, it is commonly accepted that as urea and solute concentrations are lowered during dialysis, the osmotic flow to cells throughout the body, including the brain, is disrupted, leading to mild cerebral oedema that may take several hours or days to clear (Zepeda-Orozco & Quigley 2012). These cellular changes then lead to cloudiness and inability to concentrate. The present results are consistent with Costa *et al.* (2014) findings that, for some patients, some parameters of cognitive functioning are actually worse immediately following last dialysis.

More detailed analyses of any subtle shifts in cognitive impairments over the entire dialytic cycle are needed to better understand how cognitive functioning shifts during dialysis and the interdialytic interval. Unfortunately, the low rates of reported cognitive impairment in the present study make it difficult to draw a firm conclusion about the nature of the effect of time since dialysis on cognitive functioning. Additionally, though the cognitive functioning items in the electronic diary were based on standard items from the Kidney Disease Quality of Life Scale (Hays *et al.* 1994; Hays *et al.* 1997), it is not known whether this constellation of questions, their rating scales or the frequency with which they are presented represent the most sensitive, efficacious means of collecting accurate information about patients' neurocognitive state. To date, however, there is limited evidence for a valid approach to assessing subtle, momentary changes in cognitive functioning using EMA approaches, nor do any gold-standard measures of attention, orientation, recall or concentration appear to have been translated into tools suitable for experience sampling (Sliwinski *et al.* 2018). However, many of these tasks—for example, the Trail-Making Test (Reitan 1958)—lend themselves well to adaptation for use on mobile, electronic devices such as those used in the present study. Sliwinski *et al.* (2018) have developed and evaluated a system of ambulatory cognitive assessment, tested in a sample of healthy adults, which prompted respondents to engage in Symbol Search, Dot Memory and n-Back memory tasks. They found that two of the three tasks (symbol search and dot memory) were significantly correlated with age, and all tasks were significantly correlated in the expected direction with clinic measures of cognitive functioning. Such task-oriented measures of cognitive function may prove to be the best way to measure subtle, momentary changes in cognitive functioning over relatively short periods of time.

It may also be the case that patients are not the best source of information about their own cognitive status, especially given the high level of burden and demand placed on them by their kidney disease diagnosis and treatment requirements. It might be helpful to have corroboration from a partner or family member about the perceived level of confusion, disorientation and forgetfulness of the patient on and between dialysis days. Future studies might investigate the development and employment of more sensitive, sophisticated means of assessing cognitive functioning over the dialytic cycle among patients on HD, as well as collecting reports from significant others about patients' status.

In terms of practical significance, cognitive impairments may have important impacts on patients' ability to engage in necessary disease self-management. Keeping track of food and water intake, treatment schedules and multiple prescriptions represents an enormous cognitive burden. For example, in one study, memory problems were found to interfere with medication taking among patients who have ESKD (Williams *et al.* 2008). However, other studies have not shown an effect of cognitive impairment on treatment adherence (Alosaimi *et al.* 2016). Regardless, even the subtle, very mild shifts in cognitive functioning as evidenced in the present findings may have serious consequences for patients' health status.

STUDY LIMITATIONS

The present study had a number of limitations. First, at twenty-six participants, the sample size was relatively small, although it was generally well-balanced in terms of gender, employment status and educational background. Sample sizes in this literature tend to be small (Post *et al.* 2010; Tovazzi & Mazzoni 2012; Costa *et al.* 2014; Schneider *et al.* 2015), but have yielded informative data at the present study site (Pahl *et al.* 2010a,b). Nonetheless, it is difficult to make generalisations from such a limited number of participants.

Additionally, consistent with the overall catchment of the recruitment site, the majority of the study sample was Hispanic or Latino. Although Hispanic and Latino patients represent the largest and fastest-growing ESKD population in the United States, they may have specific risk factors for kidney failure that make them less comparable with other groups.

An additional technical limitation to the present study was the low level of experience with technology in this sample. Although technological literacy was not formally assessed in the present study, anecdotal observation by interviewers suggests that many participants and would-be participants were uncomfortable with the electronic devices used for data collection. Indeed, a key reason for otherwise interested patients to ultimately decline to participate, and for enrolled participants to withdraw from participation, was discomfort with using smartphones and tablets, an issue which has never arisen in our other samples. Additionally, though project team members carefully trained participants to use the smartphone and tablet devices and to use the electronic diary programme, adherence to the study protocol was somewhat low and often attributed to participants' inability to properly use the diary system on their own. Clinic staff later informed project team members that computer ownership and experience at the recruitment site is very low, and for many patients, the tablet computer provided to them as part of the study represented their first and/or only computer. In future studies, it might be worthwhile to assess technological literacy and acceptability of using electronic devices to better determine the skill level of participants being asked to use electronic devices, and adjust subject training approaches accordingly.

IMPLICATIONS FOR PRACTICE

HD may exacerbate cognitive dysfunction among patients. Health care professionals should be aware of the possibility of diminished cognitive capacity in the hours following maintenance dialysis, and be mindful of its potential impact on successful disease self-management.

CONCLUSION

Cognitive impairment appears to be mild in stable, young patients who have ESKD. Self-reported cognitive functioning, measured using EMA, appears to be worse shortly after the HD treatment, and improved during the long IDI. Ecological momentary assessment may be a useful tool for assessing subtle shifts in cognitive function over the dialysis cycle. Future research is needed to best understand the pattern of cognitive decline over the hours and days since last dialysis, and the best approach for making ecologically valid assessments of very subtle changes in cognitive function in this high-burden population.

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BIODATA

Shayna L. Henry, PhD is a Project Manager at the Kaiser Permanente Southern California Department of Clinical Analysis. A Health Psychologist by training, her research focuses on healthcare delivery for patients with chronic kidney disease as well as the implementation of programmes designed to improve care for patients with chronic and end-stage kidney diseases.

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Table 1:

Participant demographics.

	Participants (n = 26)	%
Ethnicity		
White	2	7.7
African American	1	3.8
Hispanic/Latino/a	17	65.4
Asian/Pacific Islander	3	11.5
Native American	2	7.7
Other	1	3.8
Language spoken		
English	19	73.1
Spanish	7	26.9
Marital status		
Married	11	42.3
Unmarried	15	57.7
Education level		
Less than high school	5	19.2
High school	10	38.5
Some college	5	19.2
College degree or greater	5	19.2
Unknown	1	3.8
Employment status		
Part-time	3	11.5
Full-time	2	7.7
Disabled	8	30.8
Unemployed	5	19.2
Homemaker	3	11.5
Retired	2	7.7
Student	1	3.8
Unknown	2	7.7
Insurance status		
Medicare only	5	19.2
Medicaid only	7	26.9
Medicare + Medicaid	12	46.2
Privately insured	2	7.7

Note. Many participants listed their employment status as both disabled and unemployed. Disability status trumped other reported employment status, to distinguish those patients who were or considered themselves to be unemployed due to disability rather than unemployed but potentially interested in working.

Table 2:

Mean levels of momentary cognitive dysfunction across all monitoring days.

	Mean	SD
Slowed reaction time	.27 (out of 5)	.77
Trouble thinking	.36	1.1
Confusion	.12	.49
Difficulty making decisions	.12	.51