

ASSESSING COGNITIVE DYSFUNCTION IN THE
HEMODIALYSIS POPULATION

BY

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THESIS

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ABSTRACT

Patients with end stage renal diseases (ESRD) requiring hemodialysis treatment experience cognitive impairment due to a variety of risk factors; most of which stem from chronic kidney disease (CKD) and the dialysis process itself. The purpose of this study was to assess changes in cognitive functioning in maintenance hemodialysis (MHD) patients during a standard hemodialysis (HD) session. MHD patients (n=12) were recruited from local dialysis clinics. Cognitive function was measured using a battery of tests from the CogState and Count Battle programs at 0, 1, and 3hrs into a standard HD treatment. In addition, quality of life and depression questionnaires, heart rate, blood pressure, relative blood volume (BV), hematocrit (HCT), and O₂ saturation data was collected for comparison. Significant declines were seen in cognitive domains; specifically long term memory measures over the course of a dialysis session ($p < 0.05$). A trend toward significance was seen in the cognitive measure of working memory and the cardiovascular measure of mean arterial blood pressure. The change in several hemodynamic variables (mean arterial blood pressure, hematocrit, and relative blood volume) were correlated with the change in several measures of cognitive function. In addition, questionnaires evaluating quality of life and depression were correlated with measures of cognitive function. These findings suggest that cognitive impairment in hemodialysis patients is most likely due to a variety of cerebrovascular problems caused by CKD and the hemodialysis process itself. Further studies are needed to determine if other domains are also affected and to pinpoint the primary mechanisms behind these cognitive issues.

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CHAPTER 1

INTRODUCTION

End stage renal disease (ESRD) patients who are required to receive MHD are at high risk for cognitive dysfunction due to various risk factors, which will be discussed in depth. Murray et al. (2007) found that 70% of MHD patients ages 55 years old and older exhibited moderate to severe cognitive impairment, yet few patients had a medically-documented history of impairment. Despite growing concerns regarding the prevalence and severity of cognitive impairment in the HD population, a paucity of literature exists.

The risk factors hypothesized to contribute to cognitive dysfunction in this population can be broken into two categories: vascular and non-vascular. Cognitive function is mediated in part by cerebral blood flow, which is significantly affected by large vessel disease and small vessel disease (Pereira et al., 2005). The degradation of blood vessels in the brain limits blood flow, decreasing oxygen delivery to affected areas of the brain, and ultimately decreases oxidative metabolism. Large and small vessel disease can also be caused and/or exacerbated by other traditional cerebrovascular risk factors such as older age, hypertension, diabetes, and dyslipidemia. In addition, some nontraditional factors such as elevated plasma homocysteine levels, oxidative stress, and inflammation may also contribute to cognitive declines in this population (Pereira et al., 2005).

HD treatment results in significant acute cognitive declines (Murray et al., 2007). This is thought to occur for several reasons including rapid changes in blood pressure occurring during regular HD treatment and the high prevalence of vascular disease in the population. Giang et al. (2012) looked at the relationship between blood pressure and cognition in HD patients by analyzing systolic and diastolic blood pressure, pulse pressure, and intradialytic change in

systolic blood pressure. They found that performance on cognitive tests, specifically executive function and processing speeds, was worse in those with low diastolic pressure and a high pulse pressure (Giang et al., 2012).

The MHD process itself has been associated with increasing accounts of cerebral ischemia. A study of 151 MHD patients who had suffered acute strokes found that approximately 34% of infarcts happened within 30 minutes after a dialysis session (Murray et al., 2013). Using Xenon inhalation scans and transcranial doppler sonography, researchers found a significant decrease in cerebral perfusion and blood flow velocity after HD compared to before (Murray et al., 2013). Similarly, others have shown decreased post-dialytic cerebral oxygen metabolism using PET scans (Murray et al., 2008). While research is limited, these suggest that HD treatment acutely reduces blood flow and, therefore, oxygen consumption and brain activity.

Acute cognitive declines during HD are a significant barrier for clinicians, as much of the medical and dietary counseling patients receive occurs during treatment sessions, which may result in poorer adherence to recommendations. Indeed, a study by Kutner (2001) observed that at least 50% of HD patients are likely to be non-adherent with at least one aspect of their treatment plan. Moreover, compliance with diet and fluid intake recommendations may be as low as 35.5% and 40.3%, respectively (Lee et al., 2002). The low compliance commonly observed in HD patients may be, at least partially, attributed to receiving instruction during treatment, a time when cognitive functions such as memory and executive function are impaired.

Current practice in Nephrology includes counselling patients during MHD treatment; however, this may not be the best course of action. Murray et al. (2007) observed significant declines in cognitive function during hemodialysis which may result in significantly poorer recommendation adherence due to decreased comprehension of medical prescriptions and advice

given by practitioners during this period. To date no study has investigated cognitive function over multiple time points during a single HD session and none have given a battery of cognitive tests. Most previous studies have assessed cognitive function on off-dialysis days, before and after an HD session, or at time points across multiple HD treatment sessions. It is necessary to complete testing at various time points during a single session to truly capture intradialytic changes and eliminate confounding factors that may occur from one HD treatment to the next. Also, a battery of tests needs to be constructed and validated to reduce time, patient burden and learning effect overall since traditional tests can take upwards of an hour to complete in order to capture all necessary domains.

The study by Murray et al. (2007) has provided a sound rationale for this study and has created a stepping stone to build upon. In their study, cognitive assessments were done on four different dialysis days in an attempt to reduce patient burden due to the length of time associated with the cognitive assessments used. In addition, two of the four testing sessions were not completed in the dialysis setting, one being an hour before the dialysis session started and another 24 hours after the session had ended. This change in setting may result in drastically different results cognitively.

Despite these concerns regarding the prevalence and clinical significance of cognitive deficits in HD patients, to date there are limited studies consistently showing these deficits are occurring and, in addition, the ones that have been conducted use traditional paper and pen cognitive tests that can be both time consuming and a burden to patients. It is the goal of this study to show that there is a significant proportion of the HD population that suffers from cognitive dysfunction during treatment and that a combination of various technologies can be used to illustrate this phenomenon while minimizing patient burden and time.

CHAPTER 2

LITERATURE REVIEW

Chronic Kidney Disease: Overview

Chronic kidney disease (CKD) is an inflammatory disorder that is both progressive and pervasive; it affects about 13% of adults in the United States and this number is continuously increasing (Coresh et al., 2007). In order to reach stage 5, which is also known as kidney failure, one must have a glomerular filtration rate (GFR) $< 15 \text{ mL/min/1.73m}$ and is normally treated with dialysis or transplantation. The two leading causes of CKD, diabetes and hypertension, currently afflict 26 million Americans are currently (United States Renal Data System, 2007). CKD is associated with a variety of disturbances in serum creatinine, blood urea nitrogen, urine protein, parathyroid hormone, calcium, phosphorus, and potassium and decreases in hemoglobin and serum albumin. Even the act of dialysis can lead to complications like large fluctuations in heart rate, blood pressure and flow, oxygen delivery which can lead to cognitive impairment. Being that MHD treatment is a complicated process that involves remembering a variety of medications, fluid and dietary instructions, and appointments with various clinicians, it is imperative to attempt to minimize any reductions.

What Is Cognitive Dysfunction?

A patient can fall on wide spectrum of cognitive dysfunction. On the more severe end, decreases in cognition can be attributed to dementia; two of the most common forms being Alzheimer's disease and vascular dementia. For the HD population, cognitive issues are more likely to be linked to vascular disease (Pereira et al., 2005). Dementia is defined as a general decline from a higher point of cognition and changes in behavior due to reductions in cognition that prevent normal daily functioning. In order for cognitive impairment to have occurred, a

deficit has to have occurred in at least two areas of cognition, including memory, executive functioning, attention, speed of information processing, motor abilities, or language (Madero et al., 2008). On the less severe end of the spectrum, mild cognitive impairment may be similar to dementia but differs in that daily life is not impacted as greatly. It is imperative to diagnose cognitive dysfunction early; if one has mild cognitive impairment they are ten times more likely to develop dementia compared to a healthy individual (Pereira et al., 2005).

Prevalence of Cognitive Dysfunction in the Hemodialysis Population

As previously stated, there are few detailed studies regarding cognitive function in the HD population and the prevalence of cognitive dysfunction has not been solidified. A study by Murray et al. (2006) assessed cognitive function in 338 hemodialysis patients aged 55 and older. These patients underwent a 45 minute battery to assess memory, executive function, and language. In terms of their impairment, 13.9% were determined to have mild impairment, 36.1% had moderate impairment, 37.3% had severe impairment, and only 12.7% had no impairment. In addition, only 2.9% had any history of impairment recorded. Other early studies have reported moderate rates of impairment but tend to exclude individuals with stroke, severe comorbidities, and older populations, which is a large proportion of the dialysis population. One study assessed 80 individuals executive functioning and memory, finding severe impairment in 38% and 33% of them respectively (Murray et al., 2008).

The lack of diagnosis of impairment in CKD and HD patients is pervasive. According to the 2006 USRDS annual data report, dementia is slightly higher in CKD populations at 7.6% than HD at 7%. As the age increases to 85 and up, the impairment also increases to 16.8% with CKD and 11.0% with HD (Murray et al., 2008). Many studies show that this impairment is not being detected by clinicians. This can be seen in the Murray study and was also seen in a study

by Sehgal (1997), where only 15% of the impaired patients had precious records indicating it. Previously cited studies have cognitive impairment levels around 37% (Murray et al., 2008) but data from the USRDS has this number at only 7%.

Dementia is not used by Medicare to classify the cause of hospitalizations which is astounding considering 1,012 of 308,793 admissions in 1997 were due to dementia (Pereira et al., 2005). It can be assumed that these numbers are an underestimate since dementia does not often directly lead to hospitalizations but may lead to the inevitable cause. A study conducted in Tokyo found that the one year incidence of dementia in older patients was 4.2%, but again, this number is under-representative of the true impact (Pereira et al., 2005). Some older studies have grazed the connection between kidney function or amount of dialysis and cognitive impairments. Uremia, along with the act of dialysis itself, has been associated with poor cognitive performance when compared to controls (Pereira et al., 2005). It is clear that there is an underrepresentation of the true prevalence of cognitive dysfunction in the CKD and MHD populations.

Brain Changes in the Hemodialysis Population

Cognitive impairment may have a vast array of symptoms and underlying issues but ultimately they result from altered brain structure and metabolism. It has been observed via autopsy that stage 5 CKD patients who do not undergo dialysis present with acute necrosis of the granular layer of the cerebellar cortex, atrophy of the cerebellar cortex, and degradation of the brain stem (Pereira et al., 2005). A recent study by Kamata et al. (2000) analyzed the brains of 56 HD patients and 42 controls finding that brain atrophy index and ventricular area index were higher in HD patients; atrophy increased as dialysis time increased. This would lead one to believe that either kidney failure or HD itself may be associated with cerebral atrophy and time on HD leads to greater atrophy. Savazzi et al. (2001) correlated high levels of cerebral atrophy

with a creatinine clearance of 10 mL/min or less in 77.5% of MHD patients. They concluded that early atherosclerosis and related hyperperfusion may be the cause of cerebral damage in uremia.

Magnetic resonance imaging (MRI) has also been used to analyze the effects of CKD and HD on the brain, but in a limited capacity due to the expense and complication associated with using MRIs. Fazekas et al. (1995) compared 30 HD patients with 24 controls and found more cerebral atrophy in those undergoing HD. In addition, multiple white matter hyperintensities which show small-vessel disease, were prevalent in 33% of patients. It was also found that enlargement of the third ventricle and temporal horns were markers of cognitive impairment but not ischemic lesions (Fazekas et al., 1995). Another study found that focal white lesions were present in 56% of HD patients while only 27% of controls of a similar age presented with them (Geissler et al., 1995). Suzuki et al. (1997) used MRI to evaluate CKD patients and found white matter hyperintensities in a larger number than when compared to controls without kidney disease. These intensities were associated with hypertension, along with age and history of smoking as risk factors. Lastly, brain infarcts have been associated with two times the risk of developing dementia in HD patients (Pereira et al., 2005).

Various studies have looked at the association between kidney failure and metabolic abnormalities in animals but not much has been done with humans. These studies have found kidney failure can lead to issues using adenosine triphosphate, increased brain calcium content, altered brain cell permeability, and amino acid abnormalities (Pereira et al., 2005). Clearly, it is necessary to see if these findings translate over to humans with kidney failure. It can be concluded from these studies that the brain in an individual with CKD or undergoing HD can incur severe damage and plays a direct role in cognitive impairment.

The Hemodialysis Process and Cognitive Dysfunction

A major concern that is starting to invade HD cognition talks is concerning the dialysis process itself and its potential contribution to impairment due to recurring cerebral ischemia. Toyoda et al. (2005) looked at 151 HD patients over the course of 22 years and found that 34% of infarcts happened within 30 minutes of a dialysis session. In addition, these infarcts were 15% more likely to occur in an HD patient than someone with normal kidney functioning. It was discovered that there were significant decreases in cerebral perfusion and blood flow velocity after dialysis compared to before using Xenon inhalation scans of cerebral circulation (Gottlieb et al., 1987). In addition, positron emission tomography (PET) scans have shown decreased cerebral oxygen metabolism and regional blood flow in HD patients (Kanai et al., 2001).

It has been proposed by Murray et al. (2008) that cerebral function declines due to acute fluid shifts and intravascular volume during dialysis causing cerebral edema and decreased cerebral blood pressure, blood velocity, and cerebral perfusion. It is within reason that if these factors increase the risk of ischemia and stroke, that the rise would be correlated with increasing dialysis dosage, or Kt/V , which was supported by the Murray study which found that a $Kt/V > 1.2$ was associated with severe cognitive impairment. This raises the question of whether or not a slower ultrafiltration rate should be used along with longer dialysis sessions in order to minimize the risk of cerebral edema and recurrent ischemic episodes which ultimately lead to cognition issues.

Cognitive Dysfunction: Risk Factors Overview

Community-based studies have been conducted in the general population in order to get an idea of what the risk factors for cognitive impairment are. These include older age, female gender, low education, race, diabetes and hypertension, lipids, stroke, anemia, head trauma,

obesity, inflammatory factors, and a few genetic markers such as APOE₄ (Murray et al., 2008). Like many other health concerns, a healthy lifestyle can often protect against cognitive impairment. A diet made up of fruits, vegetables, and Omega 3 fatty acids and adequate levels of physical activity fall into this protective category (Murray et al., 2008).

The HD and CKD populations can draw parallels to the general population with the addition of stroke, cardiovascular risk factors, uremia, anemia, metabolic disturbances, and hemodynamic instability all thought to play roles. A Health ABC study found that CKD attributed 10% of cognitive impairment risk that was not explained by demographics and comorbidities (Murray et al., 2008). Dementia has been found to be associated strongly with stroke, low education and an equilibrated Kt/V ≥ 1.2 in the CKD and HD populations (Murray et al., 2008). The HD population also has high rates of hypertension, 80%, and diabetes, 60%, elevated levels of inflammation, and cardiovascular/vascular events that can lead to cognitive impairment (Murray et al., 2008). These vascular issues seems to have the highest correlation with cognitive impairment in the HD and CKD populations.

Cognitive Dysfunction: Causes and Mechanics

Vascular Risk Factors

The primary risk factor that may drive cognitive impairment in dialysis patients involve vascular issues. It has been demonstrated that cognitive functioning in older populations is connected to cerebral blood flow, and large/small vessel disease. As previously mentioned, older age, hypertension, diabetes, and dyslipidemia are traditionally recognized as risk factors (Pereira et al., 2005). There are other risk factors that could also play a role in cognitive impairment; these include plasma homocysteine (tHcy) levels, oxidative stress, and inflammation (Pereira et

al., 2005). All of these factors greatly affect cognition in the general population and may also relate to HD patients.

Cerebral Risk Factors

It has been demonstrated that age, hypertension, diabetes, and dyslipidemia are risk factors for dementia in the general population; it has also been shown that hypertension and diabetes are risk factors for stroke (Pereira et al., 2005). There is limited data, however, relating these risk factors to cognitive impairment in the HD population. A study by Sehgal et al. (1997) looked at 336 HD patients and found that a variety of factors including age, male sex, race, education, and the presence of cerebrovascular disease or depression were correlated with lower Mini-Mental State Examination (MMSE) scores. Further analysis is required to narrow the scope of these factors.

Other Potential Vascular Risk Factors

It has been suggested that factors such as plasma tHcy levels, increased oxidative stress, and inflammation increase the risk of developing cognitive impairment. Traditionally, dialysis patients present with elevated tHcy levels, greater than 1.87 mg/L, compared to the general population. This can be seen with 85% of the HD population having elevated levels while only 10% of the general population have these high levels (Pereira et al., 2005). It has been theorized that tHcy levels effect cognitive impairment via a prothrombotic affect leading to large/small vessel disease, a neurotoxic effect via the *N*-methyl-D-aspartate receptor leading to cell death, and conversion of tHcy to homocysteic acid leading to an excitotoxic effect on neurons (Pereira et al., 2005). Previous studies that have associated tHcy with cognitive impairment in the general

population. One of these showed that increased tHcy levels are predictive of Alzheimer's disease during an 8 year follow up of 1,092 patients (Seshadri et al., 2002).

Oxidative stress and inflammation are pervasive issues in the HD population that lead to a variety of other health issues. HD patients undergo oxidative stress due to reduced antioxidants and increased pro-oxidant factors (Locatelli et al., 2003). Oxidative stress and inflammation are known to contribute to atherosclerotic cardiovascular diseases, but to our knowledge, no study has been conducted connecting them to cognitive impairment. In the general population, Berr (2002) studied 1,611 healthy adults and showed that those with higher thiobarbituric acid reactant substances (TBARS), which indicate lipid peroxidation, were 2.3 times more likely for cognitive decline. In a study conducted by Schmidt et al. (2002), it was discovered that midlife C-reactive protein levels predicted the development of vascular dementia and Alzheimer's disease. These studies may not have been conducted in HD patients, but they lead one to believe that they may be associated with the mechanics of cognitive impairment in the population.

Nonvascular Risk Factors

Nonvascular risk factors such as anemia, erythropoietin (EPO) deficiency, and parathyroid hormone activity may also play a role in cognitive impairment. The majority of dialysis patients are anemic due to lack of erythropoietin production by the kidneys (Pereira et al., 2005). This may lead to cognition issues because a lower hematocrit leads to decreased brain oxygenation. A decreased hematocrit leads to a correction resulting in abnormally high cerebral blood flow carrying uremic toxins, and this higher blood flow may cause increased intracranial pressure and brain edema (Pereira et al., 2005). It has been demonstrated in animals that EPO has a neuroprotective quality and is upregulated during hypoxic events (Sun et al., 2004). It is

unknown, however, if EPO deficiency is a risk factor of cognitive impairment without anemia. Parathyroid hormone (PTH) is not well understood but may have cognitive implications. In a uremic patient, when a patient has increased PTH levels the calcium in tissues such as the brain and blood vessels is also elevated. This may indicate that PTH acts as a facilitator for calcium movement into tissues which would then affect cognition (Fraser, 1988). Since calcium is an integral factor in neurotransmission in the central nervous system and intracellular enzyme systems, it could mean that increased brain calcium content could disrupt either of these and lead to cognitive issues.

Cognitive Dysfunction: Impact on Outcomes

One of the most important aspects associated with HD and cognitive impairment is the long-term effects and ultimately expected outcomes. Dementia can often lead to a multitude of adverse outcomes. Hospitalizations are increased in those with dementia in the USRDS population (“United States Renal Data System”, 2005). One study conducted by the USRDS found that when comparing CKD patients with dementia to those without, the lifespan after starting dialysis was 1.09 and 2.7 years, respectfully (Kurella et al., 2006). In addition, death was 1.48 times as likely when dementia was present. Dementia also had a rather large impact on financial burden with an extra \$19,100 being spent by Medicare in 2002 over a year on HD patients with dementia compared to those without (“United States Renal Data System”, 2005). By reducing or removing cognitive deficits in the MHD population, one would increase the average lifespan of a MHD patient and reduce the financial burden associated with care.

Cognitive impairment can have widespread negative effects on those afflicted by it. MHD patients may have trouble understanding all the complicated aspects of their care including their dialysis sessions, diet, fluid restrictions, rationale behind their clinicians’ decisions, and

even negate their ability to provide informed consent. Cognitive dysfunction leads to diminished quality of life. Many studies have shown that HD patients have a reduced emotional well-being and psychological functioning (Bremer et al., 1995). These studies have not examined how this may connect to cognitive functioning.

Cognitive Dysfunction: Depression

Compiled with extrinsic factors that may also contribute, the HD process and cognitive impairment resulting from it may also cause depression. Agganis et al. (2010) measured a battery of neurocognitive tests and associated them with depression scores via the Center for Epidemiologic Studies Depression Scale (CES-D) in 241 MHD patients and found that the patients with higher depression scores performed worse on processing speed and executive functioning. Additionally, Ku et al. (2012) found that depression in those with chronic renal failure and uremic peripheral polyneuropathy was affected by a variety of psychological factors illustrated by the Mental Component Summary. Taken together, these results suggest that depression is another co-morbidity in HD patients associated with cognitive function.

Counters to the Argument

There are a few studies that have refuted some of the relationships that have been proposed to exist between dialysis and cognitive impairment. Dialysis adequacy, an average of Kt/V assessments, and cognitive functioning, a neurocognitive battery during the first hour of dialysis, were examined by Giang et al. (2011). In opposition to previous studies, they found that reductions in Kt/V were not associated with impaired cognition. As previously stated, various risk factors have been proposed, if not shown, to be connected to cognition. Tamura et al. (2010) concluded that cognitive impairment is common but is not associated with many ESRD and

dialysis associated risk factors; these factors include urea clearance, nutritional markers, hemodynamic measures, and anemia. These studies have only looked at a fraction of the possible risk factors and none have focused on the vascular and cerebrovascular factors that reduce blood flow, cerebral oxygenation, and ultimately cerebral metabolism.

Use of Laptop/Tablet for Assessment

Until very recently, cognitive assessments have been conducted with a “paper and pen” method that is both time consuming, lacks repeatability, and is fraught with human error. There is currently a push to incorporate more technology into cognitive assessments with positive results. One specific program is CogState, a series of predefined batteries that take place on a laptop. Previous research has validated the four standard psychological paradigms that have been defined within CogState’s brief battery by comparing healthy adults to individuals with mild head injury, schizophrenia, and AIDS dementia complex (Maruff et al., 2009). They concluded the program to have strong correlations in the measures of processing speed, attention, working memory, and more (Maruff et al., 2009). Lim et al. (2012) further validated CogState by comparing healthy older adults and patients with mild cognitive impairment, finding that it could be used to screen for Alzheimer’s related cognitive changes. Other similar computer based batteries have proven effective in detecting mild cognitive impairment in the elderly (Dwolatzky et al., 2003). CogState has also been used in association with Alzheimer’s neurodegenerative imaging markers. Mielke et al. (2014) found that CogState showed as much variance in neuroimaging measures as standard neuropsychological tests. Specifically, slow reaction times in tasks such as the Identification and One Back were associated with FDG-PET hypometabolism and slower times in the Groton Maze Learning were associated with smaller hippocampal volumes; both of which are early markers of Alzheimer’s disease (Mielke et al., 2014). Even

though CogState has not been validated in the dialysis population, evidence demonstrates that it will still be able to detect any performance deficiencies like it can with similar populations, i.e. Alzheimer's and dementia.

CHAPTER 3

METHODOLOGY

Subjects

Twelve patients on MHD (4 females, 8 males) were recruited from the Champaign-Urbana Dialysis Clinic (Champaign, IL). Patients were screened for eligibility by administering a health and medical history questionnaire. All participants gave written informed consent and this study was approved by the University of Illinois Institutional Review Board. Inclusion/exclusion criteria for patients included the following: 1) Subjects must have received MHD treatment at least 3 days per week. 2) Subjects must be between 20-75 years of age. 3) Patients on dialysis treatment for < 3 months were excluded due to physiological changes that typically occur at the onset of dialysis. 4) No previously diagnosed case of any cognitive dysfunction including but not limited to: dementia, amnesia, Alzheimer's disease, Parkinson's disease, and epilepsy.

Study Design

Following recruitment and screening, eligible participants completed two pre-testing questionnaires, the Kidney Disease Quality of Life Instrument (KD-QOL) and Center for Epidemiologic Studies Depression Scale (CES-D). Participants were given test instructions and allowed to acclimate to the tests prior to the testing day.

Twelve participants aged 20-75 years underwent a battery of cognitive tests at three time points (BASE, 1HR, and 3HR). The 1HR time point was chosen because it has been demonstrated to represent the time point during dialysis with the greatest cognitive deficits based on previous research (Murray et al, 2007). The participants were prepared for testing 15 minutes prior to the first test.

On the testing day, each participant arrived 30 minutes prior to their regularly scheduled treatment. During this time, the participants were reminded of the instructions for the various tests. A battery of cognitive tests were completed as described below at the start, 1hr and 3hrs into the HD treatment.

Cognitive Testing

Cognitive assessments included four tests from the CogState program carried out via laptop (“Home - CogState”, 2013): the chase task, the detection task, the identification task, and the international shopping task with a delayed recall; and the Count Battle program, carried out via iPad.

The Chase Task

The Chase task takes approximately thirty seconds (based on average time in healthy volunteers) and measures visual motor function. In this task, the participant was shown a 10 x 10 grid of tiles on the computer. The participant was asked to tap the blue tile in the top left corner of the grid with the cursor. As the target moved, the participant ‘chased’ it by tapping on the tiles one at a time. The subject could not move diagonally and could not skip a tile. If the participant made a mistake, they needed to go back to the last correct tile. For this task, the primary outcome was the total number of correct moves made per second, a higher score meant a better performance (Chase Task, n.d.).

The Detection Task

The next task was the detection task, which takes approximately two minutes to complete and tests psychomotor function, as well as speed of processing. Speed of processing measures how an individual can evaluate and act upon a stimulus (“Home - CogState”, 2013). The prompt for this task was: “Has the card turned over?” Initially, a playing card appeared on the screen. The card then flipped over so it was face up. As soon as it did, the participant needed to press the “Yes” button on the mouse. The card went to the back of the pack and the participant pressed the “Yes” button as soon as the next card flipped over until the practice ended. The participant practiced until they reached the required number of responses, or until the practice period expired. The real test then followed, which was the same as the practice. The primary outcome measure for this task was speed of performance, or the mean of the log₁₀ transformed reaction times for correct responses where a lower score meant a better performance (Detection Task, n.d.).

The Identification Task

The third task was an identification task, which takes approximately two minutes and assesses visual attention and vigilance. This task is relevant given the education and counselling MHD patients during treatment as well as the visual attention needed to get home post HD. The initial prompt for this task was: “Has the card turned over?” Initially, a playing card appeared on the screen. The card then flipped over so it was face up. As soon as it did this the subject needed to decide whether the card was red or not; if it was red he/she pressed “Yes”, if it was not red he/she pressed “No”. Just like the Detection Task, a practice session was first followed by the real test. The primary outcome measure for this task was speed of performance, or the mean of

the log₁₀ transformed reaction times for correct responses where a lower score meant a better performance (Identification Task, n.d.).

The International Shopping List and Delayed List Tasks

The International Shopping List Task and the Delayed version take approximately 7 minutes total due to it being done twice; once at the beginning of each testing session (5 minutes) and then a shorter version at the end of the cognitive tests for a delayed recall (2 minutes). In this instance, verbal learning and memory are the domains that are measured; specifically working memory and longer term memory (“Home - CogState”, 2013). For the initial task, the test supervisor read the list of words, 16 total, as they appeared on the computer screen at a rate of one word every two seconds. When the test supervisor finished they asked: “Tell me as many of the items on the shopping list as you can remember?” As the participant recalled words, the test supervisor clicked the appropriate button on the screen. If the participant said a word that was not on the list, the test supervisor clicked “Other Word”. If the participant repeated a word, the test supervisor clicked the word as many times as the word was said. This is repeated two more times before moving onto the next Task. The primary outcome for this task was the total number of correct responses made in remembering the list on three consecutive trials at a single session; a higher score meant a better performance (International Shopping List Task, n.d.). For the Delayed International Shopping List task, the participant was not read the list again but was simply asked to recall the previously read list. Again, the primary outcome for this task was the total number of correct responses made in remembering the list but this time after a delay; a higher score meant a better performance (International Shopping List Task – Delayed, n.d.). It is important to note that at the three different time points the list differed, i.e. 16 different words.

Count Battle

The Count Battle program uses the traditional Trail Making Test (parts A and B) but simplifies its delivery by incorporating a tablet. Normally, the task requires a subject to connect 25 consecutive dots on a sheet of paper or computer screen and the test taker needs to connect them in sequential order. In this program, participants connected 16 numeric dots in chronological order or 8 numeric and 8 alphabetic dots in the order: 1, A, 2, B, 3, C, etc. On the very easy setting the dots were static. On the easy setting, the dots would randomly shift position on the screen in set intervals. This was the same for the Normal easy setting with faster intervals. If a mistake was made, the participant needed to go back one dot; for example a mistake at 8 would set the participant back to 7. Tests were carried out at two different settings (numeric and alpha numeric) at three difficulties (very easy, easy, and normal) for a total of six tests per time point.

Cardiovascular Measurements

Research staff measured brachial blood pressure using the automatic digital blood pressure monitor in duplicate at each of the three cognitive testing points. If these two measurements were within 10% of each other, the average of the two measurements was taken as the final recorded blood pressure. If not, a third measure was taken, and the two closest measures were averaged. These measures were then used to calculate mean arterial blood pressure (MAP) for analysis.

Blood collection

All blood draws explained below took place at the clinic during regular dialysis sessions, with the assistance of the nurses and dialysis technicians. Because all dialysis patients have arterial lines in them during their dialysis treatment, the following blood collection will not require additional needle sticks. At time point zero at the clinic, subjects will have blood drawn at 2 time points: immediately prior to the initiation of dialysis treatment and 3 hours into treatment (~ 40ml total). The whole blood samples will be centrifuged and separated into 4 vials (500 μ l aliquots) that will be stored at -80°C for future analysis. The blood that is collected will be centrifuged to collect serum and plasma, which will then be aliquoted and stored at -80C until analyzed. Plasma and serum samples will be used to measure circulating levels of lipids and proteins related to co-morbidities in hemodialysis patients, including markers of inflammation and oxidative stress.

Relative Blood Volume and Hematocrit

The Critline is a regular part of dialysis treatment at the C-U clinic. The Critline non-invasively measures hematocrit, relative blood volume, and oxygen saturation in real time. A disposable blood chamber will be added to the dialysis machine by a trained staff member of the CU Dialysis Clinic. As blood travels through this chamber hematocrit and oxygen saturation are measured by the absorbance and scattering of light. The hematocrit value is then used to estimate the blood volume relative to the start of the dialysis session.

Questionnaires

As previously mentioned, the KD-QoL and CES-D questionnaires were delivered prior to testing but within a week of the testing date. The KD-QoL provides individual scores for 10 metrics related to quality of life in CKD patients, while the CES-D provides a single depression score based on an analysis of 20 items.

Statistical Analyses

All statistical analyses were performed using SPSS 22.0 software (IBM, Armonk, NY) and significance was based on a two-tailed alpha value of 0.05. Data was expressed as mean \pm standard deviation (SD) unless otherwise stated. Data was analyzed using repeated measures analysis of variance (ANOVA to compare different time points of cognitive function test. When ANOVA indicated a significant main effect of time, a protected LSD was performed to determine differences between time points.). Pearson correlations were performed to determine the relationships between parameters of cardiovascular variables, questionnaires, and cognitive function.

CHAPTER 4

RESULTS

Patient Characteristics

Patient characteristics can be seen in **Table 1**. The average age for the patients in this study was 45 ± 14 years of age. It can be seen that a relatively high proportion of diabetes (33%) and hypertension (58%) were present. The majority of participants were African American (75%) followed by Caucasian (17%).

Cognitive Functioning: CogState

The cognition measurements for the five CogState tests are shown in **Table 2**. For the delayed recall of the International Shopping List, there was a main effect of time, indicating a reduction in long term memory over the course of a dialysis session ($p=0.026$). There was also a trend for a reduction in the immediate recall component of the international shopping list over time ($p=.146$), indicating a potential decline in verbal learning and working memory. There were no significant differences in the Chase, Detection, or Identification tasks over time.

Cognitive Functioning: Count Battle

The cognition measurements for the six Count Battle tests are shown in **Table 3**. There was no significance detected for any of these tests.

Cardiovascular Measurements

The cardiovascular measurements, which included heart rate and MAP, are shown in **Table 4**. There was no change in heart rate during hemodialysis; however, a trend towards a reduction in MAP was observed during the dialysis treatment ($p=.090$).

Correlation Analysis

Results from the correlation analysis that we conducted can be found in **Tables 5-7**. There was a significant correlation between the change in the Identification Task on the Cogstate program and the change in mean arterial blood pressure. In addition, there was a trend for a correlation between change in hematocrit and change in the International Shopping List Task ($p=0.15$) and Delayed international Shopping List tasks ($p=0.13$). However, no other correlations between cognitive and hemodynamic measures were detected (**Table 5**).

Significance correlations were seen between the Chase, Detection, and Identification tasks and the KD-QoL's measures of Work, as well as between the Detection Task and the KD-QoL's measure of Support ($p<.05$). However, no other correlations were found between the other cognitive tasks and KD-QoL metrics (**Table 6**).

Data from the CES-D indicated that 33% of the patients in the study had signs of depression. However, there were no significant correlation between the CES-D score and any hemodynamic or cognitive variables (Table 7).

Table 1. Subject Characteristics

Demographics	Total (n=12)
Age (years)	45 (14)
Gender (male/female)	8/4
Race (%)	
African American	75
Caucasian	17
Other	8
Diabetes (%)	33
Hypertension (%)	58

For age, data expressed as mean \pm SD

Table 2. CogState Cognition Measurements

Measure				P- Value
	Baseline	1 Hour	3 Hour	
International Shopping List Task (# of correct responses)	22.18(4.51)	19.18(4.14)	20.00(6.44)	0.146
Delayed International Shopping List (# of correct responses)	7.81(2.09)	6.09(2.81)	5.45(3.42)	0.026
Chase Task (moves/sec)	.8512(.4113)	.8483(.4475)	.7725(.4287)	0.330
Detection Task (log10(ms))	2.67(.15)	2.68(.14)	2.67(.10)	0.917
Identification Task (log10(ms))	2.85(.09)	2.85(.09)	2.87(.11)	0.177

Data expressed as mean \pm SD

Table 3. Count Battle Cognition Measurements

Measure	Baseline	1 Hour	3 Hour	P-Value
Trails A- Very Easy (s)	31.08(19.18)	25.95(13.59)	28.31(17.86)	0.185
Trails A- Easy (s)	65.64(79.12)	65.78(80.03)	64.52(80.54)	0.919
Trails A- Normal (s)	132.48(114.72)	108.07(110.96)	128.62(119.75)	0.341
Trails B- Very Easy (s)	58.87(47.39)	49.14(31.50)	47.01(29.58)	0.421
Trails B- Easy (s)	92.55(81.20)	92.88(88.23)	100.67(89.89)	0.652
Trails B- Normal (s)	176.70(117.25)	161.98(116.50)	155.47(117.08)	0.467

Data expressed as mean \pm SD

Table 4. Cardiovascular Measurements

Measure	Baseline	1 Hour	3 Hour	P-Value
Heart Rate (bpm)	80(10)	81(11)	84(14)	0.244
Mean Arterial Blood Pressure (mmHg)	105(19)	99(19)	92(16)	0.090

Data expressed as mean \pm SD

Table 5. Correlation between the change (Δ) in Cognition and Hemodynamic Measures from the Baseline to the 3 Hour timepoint

	ΔMAP	Relative ΔMAP	ΔHCT	ΔBV	$\Delta O_2 SAT$
$\Delta CogState$					
<i>International Shopping List Task</i>	.291	.414	-.526	.337	-.086
<i>Delayed International Shopping List</i>	.008	.831	-.512	.271	.165
<i>Chase Task</i>	.401	.206	-.051	-.019	-.076
<i>Detection Task</i>	.328	.374	-.003	-.033	-.088
<i>Identification Task</i>	.624*	.065	.476	-.423	.341
$\Delta Count Battle$					
<i>Numeric Very Easy</i>	.120	.101	-.068	-.285	-.140
<i>Numeric Easy</i>	-.184	-.101	.194	-.176	.362
<i>Numeric Normal</i>	-.279	-.278	-.230	.012	.294
<i>Alpha Numeric Very Easy</i>	-.216	-.260	-.294	.436	-.349
<i>Alpha Numeric Easy</i>	.226	.146	.280	-.102	.323
<i>Alpha Numeric Normal</i>	-.075	-.036	.399	-.294	.378

*p<.05

Table 6. Correlations between Baseline Cognition Measures and KD-QoL Measures

	<i>Burden</i>	<i>Cognitive</i>	<i>Social</i>	<i>Symptom</i>	<i>CKD Effects</i>	<i>Sleep</i>	<i>Support</i>	<i>Work</i>	<i>Satisfaction</i>	<i>Staff Encouragement</i>
<i>ΔCogState</i>										
<i>International Shopping List Task</i>	-.454	-.353	-.327	-.378	-.477	-.078	-.239	.216	-.103	-.243
<i>Delayed International Shopping List</i>	-.192	-.348	-.136	-.168	-.199	.217	-.108	.227	.126	-.067
<i>Chase Task</i>	-.389	.192	.240	-.002	-.515	.035	-.438	.717*	.324	.107
<i>Detection Task</i>	.443	-.422	-.159	-.151	.432	-.021	.619*	-.632*	-.220	-.103
<i>Identification Task</i>	.405	-.211	-.116	.039	.446	.098	.486	-.626*	-.035	.085
<i>ΔCount Battle</i>										
<i>Numeric Very Easy</i>	.255	.171	-.131	.278	.439	-.117	.230	-.452	.008	.291
<i>Numeric Easy</i>	.486	.212	.149	.259	.298	.080	.204	-.369	.239	.275
<i>Numeric Normal</i>	.052	-.019	-.219	.140	.362	-.210	.322	-.300	-.154	.272
<i>Alpha Numeric Very Easy</i>	.264	.355	.202	.177	-.002	.248	-.109	-.280	.381	.342
<i>Alpha Numeric Easy</i>	.464	.160	.034	.174	.157	-.042	.243	-.474	.068	.136
<i>Alpha Numeric Normal</i>	.208	.203	-.002	.387	.532	.086	.251	-.380	.047	.443

* p<.05

Table 7. Correlation between CES-D and Baseline Cardiovascular/Critline Measures

Comparison	Pearson Correlation	P-Value
Heart Rate	.259	0.417
Mean Arterial Blood Pressure	.486	0.109
Hematocrit	.199	0.607
Relative Blood Volume	-.584	0.099
O ₂ Saturation	-.361	.339

CHAPTER 5

DISCUSSION

The principal finding of this study was that specific domains of cognitive function, primarily long term memory, and possibly short term memory, appear to decline over the course of a hemodialysis session. This was demonstrated by a significant decline in the delayed recall of the International Shopping List Task, as well as a trend towards a significant decline in the immediate recall of the International Shopping List Task. Because MHD patients frequently receive important medical information and advice during their treatment, this reduction in memory could impact their ability to manage their health, so may be clinically significant.

We also examined potential mechanisms for the change in cognitive function during HD by assessing changes in hemodynamic variables, as well as their correlation with changes in various cognitive measures. It has been hypothesized that declines in cognitive function during HD treatment may be due in part to cerebral ischemia, and indeed we saw a trend for a reduction in MAP during an HD session that could influence cerebral hemodynamics. Furthermore, we found correlations between the change in hematocrit and change in the International Shopping List Task and Delayed International Shopping List Task, and in relative blood volume and mean arterial blood pressure and depression measures. These correlations suggest that changes in hemodynamic variables during a dialysis treatment may be related to the declines in cognitive function. We speculate that interventions that influence hemodynamic changes during dialysis treatment could improve cognitive function, though this hypothesis needs to be thoroughly tested in future studies.

The delayed recall of the International Shopping List Task tests verbal learning and long term memory (Home – Cogstate, 2015). This is an important domain of cognitive functioning for

dialysis patients since they get a large amount of their education on diet, exercise, medication, and their treatment during their sessions. If HD patients cannot remember this information beyond the timing of working memory, the consequences could be detrimental. The International Shopping List Task tests verbal learning and working memory (Home – Cogstate, 2015). Being that working memory is the act of remembering information for about 15-20 seconds, it is concerning that there was a trend towards significance for this Task. In today's society, people tend to rely less on their memory and more on working of lists; these lists either being written down on paper or stored in a mobile device. This could theoretically explain the initial issue of remembering the items but does not account for the near significant dip in items as time progressed.

We observed significance and a trend towards significance in performance during 2 of 5 tasks measured by the CogState program. These tasks, the International Shopping List and the delayed version of this task, could not have a learning affect associated with them since the shopping lists change every time. There is no phase during the testing where the rules need to be learned, both mental and motor, and people are used to a list memorization task due to school or daily life. The other tasks have a variety of rules and motor aspects that need to be learned for optimal performance. For this testing, there would likely be a more accurate depiction of cognitive impairment and a significance shown if the patients could practice the tests before baseline testing. In this instance the baseline testing acted as a practice session and may have decreased performance which would make the gap in performance between the baseline and 1 hour testing sessions less. Lastly, there were only 12 participants tested in this pilot study. A larger sample size would have provided greater statistical power and possibly result in significant differences in performance on additional tasks.

Performance on the Count Battle testing did not show a decline over the course of a dialysis session. The Trails A/B tests give information regarding visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning (Arnett & Labovitz, 1995). In general, this testing is the most inclusive since executive functioning is the overarching term for the control of cognitive processes, including working memory, reasoning, task flexibility, problem solving, planning, and execution. Like CogState, if a practice session was implemented prior to the baseline testing there would likely be more significance overall. This could apply more for this series of tests due to the far more complicated rules and motor functioning needed. For this testing, a max out time of 300 seconds was used in order to: 1) stay within the 15-20 minutes of testing at each time point; and 2) Decrease the burden on the patients. In this version of the Trails A/B, an incorrect answer would set the participant back one circle. So if one was at 12 and missed 13, the program would flash red and the participant would need to select 11 again. Often what occurred was that the participant would make an incorrect selection and not notice the red flash and would continue as normal. This would lead to multiple errors, sometimes going as far back as the initial selection of 1. In addition, when a max out occurred the participant would usually have been consistently making errors and ending up near the beginning of the test. Due to this, the 300 seconds may not be truly capturing the participant's times. To counteract this, number of errors should be factored into the analysis to truly illustrate what occurred or the error causing a regression in progress should be removed.

The primary measures that were collected for the cardiovascular portion of testing consisted of heart rate and mean arterial pressure. As expected, there was no change in heart rate, but there was a trend for a reduction in MAP. Since MAP gives an indication of the mean perfusion pressure across the entire cardiac cycle, one could assume that the organs and tissues

of the body are experiencing hypoperfusion, or low blood flow. This is an important finding since a high proportion of the proposed mechanisms revolve around vascular issues leading to inadequate oxygenation of the brain (Pereira et al., 2005). To get a clearer picture of the blood flow in the brain it would be beneficial to use techniques that may give an image of what is happening in the brain during dialysis as these tests are being performed. This may include MRI, Transcranial Doppler Imaging, electroencephalography, or an OxiplexTS. The Oxiplex TS is a novel, non-invasive, way to monitor tissue oxygenation and hemoglobin concentration. By using this technology, one could better associate brain oxygenation to cognitive functioning with a more direct approach.

Multiple correlations were run across all the data presented here along with questionnaires measuring quality of life, the KD-QoL, and depression, the CES-D. The KD-QoL has multiple domains that it analyzes but the only one that showed significance was the one associated with ability to work. This measure lacks the ability to give a specific reason why the participant is able to work outside of the obvious burdens of MHD. It is a logical step in the thought process, however, to think that a reduced cognitive state would contribute to an inability to perform and possibly keep a job. The CES-D showed that 33% of the participants were depressed. This is quite a high number but when correlated with the cognitive measures there was no significance. However, when the CES-D scores were compared to baseline mean arterial blood pressure significance was seen. The trend towards significance of the relative blood volume and MAP help support this. It is well known that depression often follows measures of cognitive impairment (Peterson, 2013). This makes sense when delving further into the comparisons of the Critline and cognitive measures. The reduced perfusion of blood, shown by the MAP and BV measures, shows that lack of blood flow throughout the body is associated with

depression and cognition changes. It is necessary to look at this again once more data has been collected from a greater number of participants to see if significance is seen across more domains.

In summary, we found reductions in the cognitive domain of long term memory with near significant findings in working memory. We also found that executive functioning had no significance overall. In addition, a trend toward significance was found when looking at MAP measures over the course of a dialysis session. When correlated to the cognition measures, it was found that some Δ MAP values were highly associated. Lastly, quality of life measures pertaining to ability to work were correlated to cognitive measures and depression measures was correlated with relative mean arterial pressure; being supported by near significance in in relative blood volume and mean arterial blood pressure. Further research involving individuals on HD is needed to test if these findings hold up, if not grow larger, as the power increases. It would be very useful to use a technique to directly measure oxygenation and blood perfusion in the brain along with cognition measures to get a concrete idea of the mechanics behind cognitive impairment. To our knowledge, this is the first study that has assessed cognitive functioning as it declines across a single dialysis session using concise cognitive batteries via laptop and tablet. The novelty of this study and the reduction in patient burden that the methodology creates help to aid in the implications of these findings on future research. Ultimately, more research is needed however this study clearly shows that cognitive impairment is a pervasive issue in the MHD population that must be dealt with.

CHAPTER 6

CONCLUSIONS

A number of physiological changes occur during hemodialysis treatment including: vascular factors, cerebrovascular factors, oxidative stress, inflammation, anemia, parathyroid hormone effects, and erythropoietin deficiency, can have a detrimental effect on cognition as the session goes on. Of these, the shift in blood pressure and perfusion are amongst the most detrimental to the patient. As less blood gets to cerebral tissues, less oxygen gets delivered and neuronal activity is reduced, which ultimately leads to reduced functioning of various cognitive domains via apoptosis and necrosis. Results from this study indicate the presence of cognitive impairment and correlation between changes in blood pressure and changes in cognitions.

Specifically we found that during hemodialysis treatment:

- Long-term memory is reduced
- There is a trend for a reduction in Mean Arterial Pressure
- Changes in cognitive measures and MAP are correlated
- Cognitive measures and ability to work are correlated
- There is a trend in relative blood volume and mean arterial blood pressure when correlated with depression measures as well as change in hematocrit when correlated with changes in memory measures

We have shown that from a technical standpoint:

- It is possible to capture cognitive impairment across a single dialysis session
- It is possible to use newer, computer and tablet based-technology to capture these changes; aside from the traditional paper and pen methods that take longer and have higher patient burden

Overall, these data suggest that there is cognitive impairment in the HD population and that there is a correlation between blood pressure and the cognitive changes as well as depression and changes in blood flow. In addition, the testing measures selected for this study were sensitive enough to detect the cognitive changes while minimizing time and patient burden. This study is a stepping stone for future studies that will use more participants to hopefully show an even larger impact on cognition. Future studies may be able to use these techniques to measure cognition while taking steps to alleviate the impairment that is occurring.

CHAPTER 7

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