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The Impact of Pomegranate on Memory Dysfunction after Cardiac Surgery

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The Impact of Pomegranate on Memory Dysfunction After Cardiac Surgery

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Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

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ABBREVIATIONS

CABG	Coronary artery bypass grafting
CHD	Coronary heart disease
CAD	Coronary artery disease
AD	Alzheimer's disease
LDL	Low density lipoproteins
MRI	Magnetic resonance imaging
SPECT	Single photon emission computed tomography
PJ	Pomegranate juice
PFE	Pomegranate fruit extract
PBP	Pomegranate byproduct
ACE	Angiotensin converting enzyme
PGF	Pomegranate flower
ZDF	Zucker Diabetic Fatty
ZL	Zucker Lean
DSM-IV	Diagnostic Statistical Manual – Fourth Edition
WAIS-III	Wechsler Adult Intelligence Scale-III
WMS-III	Wechsler Memory Scale-III
HVLT-R	Hopkins Verbal Learning Test-Revised
RCFT	Rey-Osterrieth Complex Figure Test
BVMT-R	Brief Visual Memory Test-Revised

ABSTRACT OF THE DISSERTATION

The Impact of Pomegranate on Memory Dysfunction After Cardiac Surgery

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Background: Studies have shown a decline in certain cognitive abilities in individuals diagnosed with heart disease of any type or etiology. This decline is observed as the disease progresses (Muller, Grobbee, Aleman, Bots & van der Schouw, 2006; Ernest et al., 2006), as well as after certain interventions, such as coronary artery bypass grafting (CABG) and heart valve surgery. In recent years, there has been a great deal of emphasis on the beneficial effects of pomegranate on health, including diseases of the brain and the heart. Few, however, have explored the impact of pomegranate on cognitive functions. Thus, the current pilot study is unique in its exploration of the effects of pomegranate on various health parameters and its possible effectiveness in reducing cognitive declines, specifically memory, after cardiac surgery. Methods: The sample consisted of 10 patients, who had undergone elective, on-pump, normothermic cardiac surgery (CABG and/or valve surgery). Participants in the treatment group were given two pomegranate (PomX) capsules (1000mg each). Participants in the placebo group were given two placebo capsules. These capsules were taken daily starting one week before and continued to 6 weeks after surgery. Subjects were administered a comprehensive battery of neuropsychological tests at each testing session (1 week before surgery, 2 weeks after surgery and 6 weeks after surgery); however, those tests only assessing memory functions were selected. Results: Results revealed that the treatment

and placebo groups performed similarly at time 3; however, the critical time period of interpatient variability seems to be from time 1 to time 2 (with higher incidences of clinical impairments for the placebo group), particularly with visual memory measures. Conclusions: Results suggest that there are fewer incidences of memory impairments from time 1 to time 2 for individuals that supplemented their treatment with pomegranate suggesting that the contents contained in pomegranate may be targeting the factors associated with early postoperative dysfunction (i.e. hypoxia, ischemia).

CHAPTER ONE

INTRODUCTION

Diseases of the heart are the most common cause of adult morbidity and mortality, followed by cancer and stroke (Mortality and Morbidity Weekly Report [CDC], 2006; Donnelly, 2008). Coronary heart disease (CHD), also called coronary artery disease (CAD), is the most common form of heart disease and is caused by the accumulation of fatty deposits in the arteries, also known as atherosclerosis. The most recent update of the American Heart Association (2007) reveals that in 2004 over 15.8 million people (approximately 7.3% of the population) were affected by CAD. Of these people, Caucasian males have the highest prevalence of CAD (9.4%), followed by African American females (7.8%) and African American males (7.1%). Of all cardiovascular diseases, CAD has the highest mortality rate. In 2004, there were 452,300 deaths caused by CAD, representing the single leading cause of death in the U.S.

In addition to CAD, valvular disease is a prevalent cause of heart disease and mortality. Valvular heart disease describes cardiac dysfunction that is caused by functional or structural abnormalities in the heart valves (aortic, mitral, tricuspid and pulmonic) (Otto, 2004). This disease can be congenital or acquired later in life through age-related degenerative processes, mechanical injury, drug or toxin-related injury, or systemic disease-related processes (Donnelly, 2008). At the beginning of the twenty-first century, the prevalence of this disease in the U.S. population was estimated to be more than 5 million people (Goldbarg, Elmariah, Miller & Fuster, 2007). According to the American Heart Association (2006), valvular heart disease is responsible for 20,000 deaths in the US and a contributing factor in 42,000 deaths each year. Out of these cases,

63 percent involved disorders of the aortic valve and 14 percent involved the mitral valve. However, deaths due to pulmonic and tricuspid valve disorders are rare.

Studies have shown a decline in certain cognitive abilities in individuals diagnosed with heart disease of any type or etiology. This decline is observed as the disease progresses (Muller, Grobbee, Aleman, Bots & van der Schouw, 2006; Ernest et al., 2006), as well as after certain interventions, such as coronary artery bypass grafting (CABG) and heart valve surgery. CABG is a surgical procedure that is used to treat individuals with CAD and to relieve angina (Klonoff, Clark, Kavanagh-Gray, Mizgala & Munro, 1998). Heart valve surgery is a procedure used to repair or replace damaged heart valves. Although the rate of mortality has been reduced with these procedures, there is growing concern about the morbidity associated with cardiac surgery. Some of these issues include stroke, depression and cognitive difficulties. Research on morbidity issues are of increasing importance as they play a role in the pursuit to improve surgical outcomes and the quality of life in patients (Symes, Maruff, Ajani & Currie, 2000).Thus, increased focus has been lent to the postoperative status of the brain and its cognitive functions after cardiac surgery (Selnes, Goldsborough, Borowicz & McKhann, 1999).

Research suggests that a majority of individuals who undergo CABG experience declines in neuropsychological functioning post-operatively. This decline has been observed in up to 80% of patients early after surgery, and in up to 30% of patients after 6 months (Knipp et al., 2004). In particular, a decline is evident with verbal memory, word fluency and psychomotor speed (Mosley et al., 2005), visual memory, processing speed and executive functioning (Muller et al., 2007), as well as attention (Almeida & Flicker,

2001). Although research on cognition after valve surgery has been limited, studies have shown cognitive declines postoperatively (Ebert, Walzer, Huth & Herrmann , 2001; Hong et al., 2008), specifically with surgery that involves valve replacement compared to valve repair (Grimm et al., 2003).

Although findings on cognitive declines have been consistent in CABG and heart valve surgery research, preventive or treatment options for cardiac surgery-related cognitive dysfunction have not been examined extensively. In recent years, there has been a great deal of emphasis on the beneficial effects of pomegranate on health, including diseases of the brain and the heart. Few, however, have explored the impact of pomegranate on cognitive functions. Thus, the current study is unique in its exploration of the effects of pomegranate on various health parameters and its possible effectiveness in reducing cognitive declines, specifically memory, after cardiac surgery.

Coronary Artery Disease (CAD) and Cognition

Cardiovascular disease (which is the umbrella term for CAD) and dementias such as Alzheimer's disease (AD) are common with increasing age (Muller et al., 2007). Recent studies have suggested that cardiovascular disease may promote β-amyloid deposition in the brain, a pathology that has incidentally been linked to an increased risk for Alzheimer's disease and its associated cognitive deficits, including memory deficits (Launer, Masaki, Petrovitch, Foley & Havlik, 1995). Research has also suggested that a decline in cognitive functioning with age may be due, in part, to atherosclerotic changes (Aleman, Muller, de Haan & van der Schouw, 2005).

Atherosclerosis has been implicated in various subtypes of dementia, suggesting that there is an association between atherosclerosis and memory dysfunction (Hofman, et al., 1997). Atherosclerosis is a disease affecting the arterial blood vessels in which an inflammatory response occurs due to the buildup of macrophage white blood cells and low density lipoproteins (LDLs, also known as "bad cholesterol") (Maton et al., 1993). An oxidized LDL forms when the lipoprotein crosses an artery wall and oxygen free radicals react with it (Kunitomo, 2007). In order to absorb the oxidized LDL, the body's immune system sends macrophage white blood cells to the artery. However, these macrophages cannot process the oxidized LDL, which causes the cells to grow, rupture and deposit more oxidized cholesterol onto the artery wall signaling more white blood cells to the area. The artery becomes inflamed and the plaque causes the muscle cells to enlarge, further causing the formation of a hard cover over the affected area. This leads to the narrowing of the arteries, reduced blood flow, increased blood pressure (Maton et al., 1993), and an increased risk of myocardial infarctions (heart attacks) and ischemic strokes.

Similar cognitive problems have also been observed in individuals without dementia. One study quantified the role of cardiovascular disease in cognitive functioning in middle-aged and elderly men. Carotid intima-media thickness (a marker of the extent of the atherosclerosis), pulse wave velocity (which reflects arterial stiffness), and ankle-to-brachial systolic blood pressure (which represents the presence of abnormalities of the atherosclerotic vessel wall of the leg arteries), were used as measures of cardiovascular disease. In addition, cognitive tests that calculated verbal and visual memory functioning, processing speed/capacity, and executive functioning were administered. Results showed

that increased intima-media thickness was associated with lower scores on memory tests and pulse wave velocity was associated with lower scores on processing capacity and executive functioning tests. It was also found that those subjects with prevalent cardiovascular disease had a poorer memory performance and lower scores on general mental status tests (e.g., MMSE) compared to the control subjects (Muller et al., 2007). A comparable study by Hanon and colleagues examined the relationship between arterial stiffness [measured by carotid-femoral pulse wave velocity (PVW)] and cognitive function in a group of elderly participants reporting memory loss. A significant association was observed between PVW and cognitive status. Specifically, they found that PVW was higher in those individuals with mild cognitive impairment than in those individuals without cognitive impairment, suggesting that functional changes in the arterial system can affect cognitive functioning and may be involved in the onset of dementia (Hanon et al., 2005).

Some conditions are considered to put individuals at greater risk for developing CAD. Research has shown several risk factors to be associated with CAD, such as total cholesterol, LDL cholesterol levels, HDL cholesterol levels, diabetes, blood pressure and smoking (Gordon, Castelli, Hjortland, Kannel, & Dawber, 1977; Gordon & Kannel, 1982). A prospective study utilized a prediction model to determine the risk factors that predict CAD in 2,489 men and 2,856 women. During the 12 years of follow-up, 383 men and 227 women developed CAD. Development of CAD was significantly associated with blood pressure (hypertension), total cholesterol, LDL cholesterol, and HDL cholesterol. This suggests that these risk factors significantly predict CAD (Wilson et al., 1998).

Studies have shown many of these risk factors for CAD are also associated with cognitive declines. For example, a number of studies have examined the effects of chronic hypertension on cognitive function and have indicated a positive relationship between hypertension in midlife and the onset of cognitive decline 15-25 years later (Elias, Wolf, D'Agostino, Cobb & White, 1993; Launer et al., 1995; Skoog et al., 1996; Kilander, Nyman, Boberg, Hansson, & Lithell 1998a; Swan, Carmelli & Larue, 1998a; Launer, 2002; Kivipelto et al., 2006). Cholesterol level and its effect on memory disorders such as dementia has also been studied extensively. Research has shown that there is an association between high cholesterol levels and dementia in middle aged individuals (Notkola et al., 1998; Kivipelto et al., 2006; Moroney et al., 1999). These results illustrate that memory functions may be particularly vulnerable to decline in CAD.

In sum, CAD may initiate β-amyloid deposition and atherosclerosis, conditions which have been implicated in memory disorders such as dementia. Memory problems have also been linked to many of the risk factors for CAD (i.e., hypertension, cholesterol). Therefore, it is reasonable to presume that memory problems would be among the most likely cognitive deficits observed in those with severe, advanced heart disease. Identifiable interventions which reduce β-amyloid deposition, atherosclerosis, hypertension and cholesterol may thus be effective at minimizing consequential memory problems.

Coronary Artery Bypass Grafting (CABG)

Coronary artery bypass grafting (CABG) is a surgical procedure used in the treatment of ischemic heart disease and to relieve angina (Symes et al., 2000). It has been found to be an effective treatment for patients with CAD, allowing sufficient blood flow

so that oxygen and nutrients can be delivered to the heart. The purpose of CABG is to restore the blood flow to areas of the heart muscle that receive an insufficient amount of blood and oxygen due to the narrowing of the arteries. During CABG, the left internal thoracic artery and the right internal thoracic artery are used for the bypass. If additional bypasses are required, a portion of the saphenous vein from the patient's leg or the radial artery from the forearm can be used as well. This vein or artery is used as a graft by attaching it at one end to the aorta. The other end is sewn to an opening in the coronary artery, beyond the blockage. The graft creates a detour that allows the blood to go around the blockage, improving the blood supply to the heart. This entire process may be done with or without a heart-lung machine. The utilization of the heart-lung machine to perform cardiopulmonary bypass is referred to as "on-pump," and not utilizing the heart-lung machine to perform cardiopulmonary bypass is referred to as "off-pump." With the heart-lung machine, the heart is stopped. The oxygen-poor blood is diverted to the machine. The machine oxygenates the blood by removing the carbon dioxide and then the oxygenated blood is returned to the heart (Horowitz, 1988).

CABG and Neuropsychological Functioning

Many studies have examined the potential effects of CABG on neuropsychological functioning. Most of these studies have examined cognitive domains such as memory, visuo-spatial perception, psychomotor speed, attention, executive function and affect (McKhann et al, 2005; Knipp et al, 2004; Selnes, McKhann, Borowicz & Grega, 2006). In a review by Selnes et al. (2006), significant early declines in memory, psychomotor speed, executive functions and visuo-spatial abilities have been observed in various studies. Notably most of the patients return to their baseline cognitive

functioning between 3 to 12 weeks. Along with objective declines in memory, subjective declines in memory have been reported as well. Subjective memory complaints are the most common grievances reported a few weeks after CABG surgery (Selnes et al., 1999). However, until recently, subjective memory complaints were not a focus of CABG research due to premature conclusions that subjective cognitive changes are more closely associated with depressed mood than objective cognitive dysfunction. Selnes and colleagues compared CABG patients with nonsurgical patients, who are at risk for coronary artery disease, on their self-reported memory symptoms over a period of 3 and 12 months. The results showed that the frequency of self-reported changes (declines) in memory, personality and reading books at 3 months was significantly greater in CABG patients than the control group. After controlling for depression, the risk for self-reported memory changes was 5 times higher in the CABG patients compared to the control group. In addition, the risk of developing new memory problems between 3 months and 12 months was 2.5 times higher in the CABG group compared to the nonsurgical controls (Selnes et al., 2004). Therefore, the study suggests that subjective memory complaints are not due to depression and are consistent with objective findings of memory declines after CABG.

Although research on early postoperative cognitive outcome has shown consistent results, there have been some inconsistencies reported in studies examining long term cognition (1-5 years) after CABG. Studies have reported that motor functions and psychomotor speed continue to be affected by CABG five years later (Selnes et al, 2006; Stygall et al., 2003). In contrast, declines in verbal learning and memory seem to diminish after five years (Stygall et al., 2003). In a small study from Germany,

researchers followed up on an initial cohort of patients after CABG. They were retested between 32 and 65 months later (median latency 55 months). A significant global decline was not reported in any of the patients (Mullges, Babin-Ebell, Reents & Toyka, 2002). However, 4 patients (8%) were one standard deviation below their baseline functioning on 2 tests. Sixteen patients (31%) had lower follow-up test scores on one test and 46 (88%) had better results in at least one of the tests. In contrast, another study reported that 42% of patients out of the 62% of patients that were available for follow-up had a decline on a global measure of cognition five years after CABG. These investigators attributed these late cognitive declines to old age, fewer years of education, and higher baseline score (and therefore, possibly regression to the mean). Importantly, those patients without cognitive impairment at discharge (7 days post-CABG) remained above their baseline level of cognitive functioning when examined five years later; however, those patients with cognitive impairment at discharge showed a marked decline from their baseline level of cognitive functioning five years later (Newman et al., 2001). Conflicting results may reflect different underlying mechanisms of deficit.

Physiological Mechanisms

One proposed mechanism for postoperative cognitive decline is cerebral ischemia. Cerebral ischemia is a lack of blood supply to areas of the brain, which may be due to hypoperfusion of the brain secondary to CAD itself or it may be due to focal occlusion (stroke) by microembolic particles released into the vasculature during surgery (Schmitz, et al, 2003). The incidence of stroke in CABG patients is 0.8-5.2% and studies have shown emboli strokes to be the most common type (Gotesman & Wityk, 2006). Postoperative cerebral ischemic injury can be assessed using diffusion-weighted

magnetic resonance imaging (MRI). MRI studies have shown that there are new focal lesions after surgery in 21-45% of patients. One study examined the effects of CABG on new postoperative cerebral ischemic lesions. The sample consisted of 101 patients undergoing on-pump and off-pump CABG surgery. The results revealed that 3-months postoperatively, nine on-pump patients and four off-pump patients had one or more new lesions, with more lesions in the middle cerebral artery territory (Lund et al, 2005). Another similar study found 45% of the patients to have 32 new ischemic lesions. Of these patients 62% had at least 2 new lesions (Knipp et al., 2004). Barber et al. (2008) found that 100% of patients with postoperative lesions and 35% of patients without lesions demonstrated cognitive declines. Additionally, the study revealed an association between the number of abnormal cognitive tests and the number and size of the lesions (termed "ischemic burden"). Hypoxia, which often occurs in conjunction with ischemia, is another proposed mechanism for post-operative cognitive dysfunction. Cerebral hypoxia is a lack of oxygen to the brain despite adequate blood flow (Kolb & Wishaw, 1996).

Recent studies have shown that hippocampal structures are directly impacted by hypoxia (Browne, Halligan, Wade & Taggart, 2003). Research findings indicate that the hippocampus contains highly vulnerable and highly resistant populations of cells (Martone, Hu & Ellisman, 2000). An episode of transient ischemia for 10-15 minutes, for example, creates a hypoxic state that leads to selective cell death in the CA1 pyramidal cells of the hippocampus, which are highly vulnerable to damage under such conditions (Schmidt-Kastner & Freund, 1991). One study examined the relationship between CABG, postoperative hypoxia, and cognitive function. The sample consisted of 115

patients undergoing CABG. Using arterial blood gas measurements, they found that five days after CABG, there was a significant correlation between postoperative cognitive dysfunction (calculated using a composite cognitive index score) and lower postoperative blood gas levels (Browne et al., 2003).

A separate study examined the effects of CABG (on pump and off pump) on cognitive functions and cerebral perfusion (blood flow to the brain) in 65 patients with CAD using single photon emission computed tomography (SPECT) imaging that captures regional cerebral blood flow images. SPECT and neuropsychological tests were performed one day before surgery, 10-14 days after surgery and six months after surgery. Of these patients, 22 patients underwent on pump, normothermic CABG surgery (group 1), 21 patients underwent on pump normothermic CABG surgery and were administered the drug instenon ("Nycomed," a drug that helps with cerebral perfusion and may prevent ischemic and hypoxic cerebral damage) (group 2), and 22 patients underwent off pump CABG surgery (group 3). Results revealed that in 68% of the patients, there was a decrease in the regional cerebral blood flow in the early postoperative period. Moreover, 96% of those in group 1, 61% of those in group 2, and 54% of those in group 3 experienced neuropsychological deficits in the early period after CABG. These patients showed significant impairments in the Trail Making Test, Rey Auditory Verbal Learning Test and the Complex Figure Test, all of which are primarily executive functioning and memory tasks. They also found that the decline in visual memory correlated with a decrease in blood flow in the early postoperative period. In the six-month follow-up, researchers found that brain perfusion was lower than the baseline in 55% of the patients. An improvement of immediate verbal memory correlated with an increase in blood flow

6 months after surgery (Chernov, Efimova, Efimova, Akhmedov & Lishmanov, 2006). After six months, the incidence of cognitive decline decreased to 55% in all of the cases combined. Not only does this study implicate cerebral perfusion as one of the causes of cognitive dysfunction, it also suggests that administered agents, such as instenon, which improves cerebral perfusion may serve to prevent decline or improve cognitive functioning. Like instenon, other preventative treatments such as pomegranate may also reduce ischemic and hypoxic cerebral damage after cardiac surgery, and thus play a role in reducing postoperative cognitive deficit. Neuron loss has been examined as a potential mechanism of post-CABG cognitive deficit as well. Rasmussen, Sperling, Abildstrom and Moller (2002) administered neuropsychological tests and measured neuron loss using SPECT in 15 patients undergoing CABG surgery. Neuropsychological testing was performed before surgery, postoperatively at discharge and 3 months after surgery. SPECT imaging was performed before surgery and 3 months after surgery. To measure neuron loss, subjects were given iomazenil, a drug that has a binding affinity for benzodiazepine receptors, and then density of the benzodiazepine receptors in the cerebral cortex was measured using SPECT. Benzodiazepine receptor density is a "measure of the number of GABAergic synapses in the cerebral cortex and is therefore assumed to indicate the intactness of cortical neurons" (pg. 1579). Cognitive dysfunction was found in 46.7% of patients at discharge from the hospital. Furthermore, there was a significant decrease in the density of neurons in the frontal cortex and in the left temporal lobe after CABG. However, the SPECT scan results did not correlate with performance on neuropsychological measures of memory, sensorimotor speed and cognitive flexibility. This suggests that there may be other causes for the cognitive dysfunction and

it may not be solely due to the loss of neuron receptors (Rasmussen, Sperling, Abildstrom & Moller, 2002).

Surgical Variables

Although the results have been mixed about the etiology of neuropsychological impairment after CABG, it has been hypothesized that the use of the heart-lung machine to conduct the cardiopulmonary bypass is a cause of cerebral injury (Roach et al., 1996). With the use of a heart-lung machine, cardiopulmonary bypass diverts blood flow to an extracorporeal circuit that maintains sufficient circulation and respiration. It basically replaces the heart and lungs in order to assist with the heart surgery (Casthely & Bregman, 1991). To avoid the morbidity associated with the on-pump technique, some surgeons are performing the off-pump technique. In this technique, a stabilizing device is used on the "beating" heart allowing the surgeon to work on the heart without the machine (Mitka, 2004).

One study demonstrated that there is a higher embolic load in those undergoing on-pump surgery than those undergoing off-pump surgery (Stroobant, Van Nooten, Belleghen & Vingerhoets, 2005). Embolic load refers to the number of cerebral emboli that travel through the blood stream, and potentially lodge in and block a blood vessel. Embolic load is calculated by counting and measuring the diameter, length and volume of the emboli (Brown, Moody, Challa, Stump & Hammon, 2000). An emboli can be a blood clot, fat, oil, bubble of air, or a mass of cells which is brought through the blood from a large vessel. The emboli is pushed into a smaller vessel where it blocks circulation. This may cause cerebral ischemia in which there is an insufficient supply of blood to the brain. This may lead to stroke or there may be a gradual decrease in blood flow causing brain

damage or death (Kolb & Wishaw, 1996). While there is some evidence of less neuropsychological impairment in the immediate postoperative period in those patients undergoing off-pump surgery (Diegeler et al.,2000; Zamvar et al., 2002), significant differences between off-pump and on-pump surgery in longitudinal cognitive outcomes have not been observed (Lund et al., 2005; Van Dijk et al., 2002).

There has also been considerable variability in surgical procedures within on-pump surgery such as cross-clamping technique, degree of hypothermia, and rate of rewarming that have been implicated as the causes of cognitive declines after CABG (Selnes & McKhann, 2005). Majority of the studies have examined differences in neuropsychological functioning in normothermic versus hypothermic cardiopulmonary bypass. The normothermic technique involves keeping the blood temperature at approximately 37°C as it passes through the extracorporeal circuit. The mild hypothermic technique involves keeping the blood temperature approximately between 32-34°C (Grimm et al., 2000). The hypothermic technique has been used in order to reduce oxygen and glucose consumption during cardiopulmonary bypass thereby protecting the cells from hypoxic ischemia (Casthely & Bregman, 1991). Some investigators have reported that they were unable to reveal an effect of systemic temperature on neuropsychological functioning (Grigore et al., 2001). Another study found that cognitive impairment was more prominent in patients undergoing mild hypothermia cardiopulmonary bypass (Grimm et al., 2000). On the other hand, other investigators have found that mild hypothermia has neuroprotective effects and there is less cognitive impairment compared to normothermic cardiopulmonary bypass (Kadoi, Saito,Takahashi, Fujita & Goto, 2004; Nathan, Wells, Munson & Wozny, 2001). Overall, surgical

techniques or modifications have not consistently controlled for cognitive impairment. Thus, there is a need and opportunity to minimize cognitive impairment via some other methodology/intervention that is perhaps not surgical.

Certain perioperative events, such as cardiopulmonary bypass time, have also been implicated as a cause of cognitive impairment after CABG. One study examined the asymmetry of cerebral embolic load and its effects on cognitive functioning found that CABG patients had a decline in verbal memory which was associated with cardiopulmonary bypass time, but not with embolic load (Bokeriia et al., 2007). Yet, other studies examining perioperative factors such as anesthesia time and surgery time have found mixed results in relation to cognitive declines. Studies have shown a postoperative cognitive decline in older adults after receiving general anesthesia during cardiac and non-cardiac surgery (Anwer, Swelem, el-Sheshai & Moustafa, 2006; Rasmussen et al., 2003), particularly in the area of memory (Williams-Russo, Sharrock, Mattis, Szatrowski & Charlson, 1995). Similarly, Moller et al. (1998) found that the duration of anesthesia was a risk factor for early postoperative cognitive dysfunction. However, one study examined elderly patients undergoing non-cardiac surgery under general anesthesia and their cognitive functioning after surgery. They found that the duration of anesthesia did not predict short-term or long-term change in cognitive functioning (Dijkstra, Houx & Jolles, 1999). A study by Ille and colleagues (2007) examined patient-related and surgery-related risk factors on cognitive performance. The study included patients that were undergoing cardiac surgery, including coronary artery bypass grafting. Results revealed that for elderly patients, older age, preexisting medical

risk factors, and surgery duration were the most important factors influencing their cognitive performance.

Individual Differences

Individual factors such as age and education have also been examined in CABG studies to determine whether these variables are associated with postoperative cognitive dysfunction. Many of the studies have shown that age, specifically increasing age, is associated with postoperative cognitive dysfunction (Tuman, McCarthy, Najafi & Ivankovich, 1992; Newman et al., 1994). Moller and colleagues (1998) found that age may be a risk factor for postoperative cognitive dysfunction 3 months postoperatively, particularly in the areas of executive functioning and memory.

Years of education of CABG patients has also been examined in many studies and has been found to be associated with cognitive decline (Moller et al., 1998; Newman et al., 2004). A study by Ho and colleagues (2004) examined various predictors of cognitive decline after CABG. They found that many medical variables as well as education were associated with cognitive decline 6 months post-CABG. Specifically, the more years of education the patients had, the less cognitive decline they had. Another study by Dupuis and colleagues (2006) examined the cognitive performance of patients before and after CABG, while controlling for age and gender variables. Results revealed that patients with less than a high school education had greater cognitive declines on tasks of attention/concentration, verbal fluency, and logical/verbal memory. However, there was one study which found that education was not a predictor of cognitive change (Selnes et al., 1999). In sum, cognitive functions (especially memory) are impacted post-operatively. Although several hypotheses have been developed to explain postoperative

cognitive dysfunction, which include physiological mechanisms (e.g emboli), surgical variables (e.g. on-pump vs. off-pump, CPB time, etc.) and individual differences (e.g. age and education), findings have been mixed.

Valvular Heart Disease and Cognition

Valvular heart disease most commonly affects aortic and mitral valves. Specifically, the five most common types of heart valve disease are mitral valve prolapse, mitral stenosis, mitral regurgitation, aortic stenosis, and aortic regurgitation. Mitral valve prolapse occurs when the leaflets of the valve become enlarged and do not close properly. In addition, when the leaflets become enlarged, they bulge into the atrium as the heart contracts and disrupt the blood flow. The mitral valve may also become displaced due to the fibrous strings supporting the leaflets becoming stretched and inflamed. Moreover, starch-like deposits are observed on the valve. The causes of this condition include coronary artery disease and Marfan syndrome. Mitral stenosis is characterized by a scarred, rigid, and calcium-hardened valve. In this case, blood cannot flow forward easily and pressure and fluid build-up are transmitted back to the lungs. The etiology of this condition is rheumatic fever, connective tissue disorders and tumors. In mitral regurgitation, or mitral insufficiency, the valve does not close properly and the blood leaks backward into the atrium. This occurs when the muscles that control the closing of the valve malfunction, the fibrous strings supporting the leaflets rupture, or if the valve degenerates. The cause of this condition includes rheumatic fever, mitral valve prolapse, coronary artery disease, and connective tissue disease. Aortic stenosis is characterized by valve degeneration and calcification, often leading to slowed blood flow. The etiology of

this condition includes congenital abnormalities, coronary artery disease, and rheumatic fever. Aortic regurgitation occurs when the valve does not close properly and blood leaks back into the ventricle. The causes of this condition include congenital abnormalities, endocarditis, rheumatic fever, connective tissue disorder and aortic stenosis (PDR Network, 2010).

Although the etiology of the two types of heart disease may be different, there are certain commonalities between valvular heart disease and coronary artery disease. Studies have found a strong association between these two diseases and have shown that 50% of valve patients have coronary artery disease (Mautner & Roberts, 1992; Peltier et al., 2003). Histopathologic evidence has also suggested that lesions in aortic valves is a process that is similar to atherosclerosis (Rajamannan, et al., 2002). Specifically, calcific aortic stenosis is mediated by a chronic inflammatory disease process that includes lipoproteins, lipids, T-lymphocytes, macrophages, and foam cells (VanAuker, 2007; Li, Hu, Liu, Tang & Huang, 2007). One study examined the incidence of coronary atherosclerosis in patients with acquired valve disorders (aortic and mitral valve). They found that patients with aortic valve disease had significant coronary lesions compared to patients with mitral valve disease (36% vs. 12.8%), suggesting that the high prevalence of atherosclerotic risk factors in patients with aortic valve disease may be similar to that of coronary artery disease (Zapolski, et al., 2004). Given the aforementioned association between atherosclerosis and cognitive functioning (and memory in particular), it is reasonable to assume memory functioning in those with valvular disease may be similarly impacted by heart disease and resulting surgical intervention.

Heart Valve Surgery (Repair and Replacement)

Similar to CABG, almost all current valvular surgical procedures require the use of the cardiopulmonary bypass machine (Otto 2004). During traditional valve surgery, the surgeon makes an incision down the center of the sternum (breastbone) in order to get direct access to the heart. There are several ways to repair valves, including separating fused valves in order to widen the valve opening, cleaning calcium deposits to allow for more flexibility and proper closure of the valves, triangular resectioning (when a portion of the floppy leaflet is cut and sewn again so that it is not in the atrium) to allow for proper closure, and patching tears or holes in leaflets to ensure proper blood flow and prevent leaks. If repair is not an option, the defective valve is removed and another valve is sewn. These replacements can be either biological or mechanical. Mechanical valves are made of synthetic durable material that is well-tolerated by the body. However, those who receive these valves require life-long treatment with a blood-thinning medication due to the incidence of blood clots in these patients. Biological valves, on the other hand, are made from biological material, including porcine (pig), bovine (cow), and human (allografts or homografts). The disadvantage of this type of valve is that it is not durable, typically lasting approximately 10 years, and thus often requires replacement. However, no blood-thinning medications are required for this type of valve (Gillinov).

Heart Valve Surgery and Neuropsychological Functioning

The impact of CABG on neuropsychological functioning has been a popular topic of empirical investigation over the past decade or two. However, research in the area of valve surgery and neuropsychological functioning is fairly recent and much more limited. However, similar etiological factors have been considered.

Individual Differences

As mentioned previously, factors such as hypertension, cholesterol, diabetes, and smoking history have been found to be associated with the development of valvular heart disease (similar to CABG). Therefore, it would be expected that cognitive declines may be due to such factors, as they are in CAD.

Physiological Mechanisms

In addition, the cascade of events (i.e., ischemia and oxidative stress) after valve surgery has also been shown to greatly impact cognitive performance. For example, studies have found rates of postoperative ischemic lesions after valve surgery ranging from 29% to 47% (Stolz et al., 2004; Knipp et al., 2005), with higher rates in those undergoing aorta valve surgery (Floyd et al., 2006). One study evaluated brain injury in valve replacement patients and demonstrated that there were new ischemic lesions. In addition, significant declines were noted in the areas of memory, attention and information processing. However, postoperative cognitive dysfunction did not correlate with the number of lesions (Knipp et al., 2005). Barber and colleagues (2008) found that of those patients undergoing valve surgery, 5% had perioperative strokes, 43% had new ischemic lesions, and 63% had cognitive decline 6 weeks after surgery. In addition, cognitive decline was associated with perioperative ischemia and greater ischemic load (Barber et al., 2008).

The types of valve replacements (biological valve prostheses versus mechanical valve prostheses) have also been an important area of study. Research has shown that mechanical valve prostheses produce significantly more cerebral emboli compared to biological valve prostheses (Georgiadis, Grosset, Kelman, Faicheny & Lees, 1994). One

study compared cognitive declines in patients undergoing biological valve prostheses and mechanical valve prostheses, by means of P300 auditory evoked potentials which is a general indicator of neurocognitive functioning and two standard psychometric tests (Trailmaking Test part A and MMSE). Results demonstrated that there was significant postoperative cognitive decline in both groups. However, there was no significance in cognition between patients undergoing mechanical or biological valve prostheses. In addition, it was found that postoperative neurocognitive decline was not reversible in patients undergoing biological valve prosthesis, but reversible in patients undergoing mechanical valve prosthesis. The researchers suggested that these results may have been due to the biological valve prosthesis patients being older in age and reversibility was determined by the severity of atherosclerosis (Zimpfer et al., 2003). More recently, the same researchers examined the long-term impact of mechanical aortic valve replacement on neurocognitive function. This study examined three time points (7 days, 4-month and 3-years postoperatively. As with the earlier study, they found that there were no adverse long term effects on neurocognitive function after mechanical aortic valve replacement (Zimpfer et al., 2006).

Grimm and colleagues (2003) compared neurocognitive brain function in patients undergoing mechanical mitral valve replacement and mitral valve repair. Neurocognitive function was measured by P300 auditory evoked potentials and two neuropsychological tests (Trail Making Test Part A and Mini Mental Status Examination). Results showed that those patients undergoing mitral valve replacement demonstrated neurocognitive damage, while those patients undergoing mitral valve repair did not show such declines (Grimm et al., 2003).

One study examined neuropsychological functioning (specifically, attention and verbal and nonverbal learning and memory) in patients undergoing CABG and valve replacement surgery at three different assessment points (before surgery, approximately a week after surgery and a month after surgery). Results showed that both groups did not differ from each other at any assessment point (Browndyke et al., 2002). However, another similar study found that patients undergoing valve replacement surgery have greater neuropsychological declines than CABG patients, particularly in the area of learning and memory (Ebert et al., 2001). It has also been suggested that new ischemic brain lesions and strokes are more frequent in patients undergoing CABG and valve surgery simultaneously, compared to those undergoing only one cardiac procedure (Newman et al., 2006).

In patients with atherosclerotic lesions, oxidative stress is a common observation. More recently, this phenomenon has been examined in patients with calcific aortic valvular stenosis. Results of directed studies have shown that there is an increase in oxidative stress in calcified regions of stenotic aortic valves. However, it has also been found that the mechanisms involved in oxidative stress are different between atherosclerotic arteries and stenotic aortic valves. Specifically, a decrease in antioxidant enzyme function has been noted in calcified stenotic aortic valves while an increase in antioxidant enzyme function has been demonstrated in atherosclerotic arteries (Miller et al., 2008). Although the mechanisms are different, the increase in oxidative stress suggests that both CAD and valvular disease have a somewhat similar pathology. Therefore, interventions which have the potential to reduce oxidative stress may prove useful in reducing negative outcomes (including cognitive decline) in both disease states.

Overall, valve disease and subsequent valve surgery appears to be associated with cognitive declines; however, there is a limited amount of data compared to CAD and subsequent CABG surgery.

In sum, there are common risk factors between the two disease states that may be responsible for some of the cognitive declines observed in cardiac patients. Research has also shown that the cardiac surgery itself may cause oxidative stress, hypoxia, ischemia and embolisms in the brain leading to significant memory dysfunction. According to a review conducted by Rasmussen (2006), studies have demonstrated that this postoperative cognitive decline is observed in non-cardiac patients, lending further support that surgery may be responsible for a major part of the memory dysfunction. Given the physiological mechanisms involved in the disease states and the surgeries, pomegranate supplementation may lower/reduce these risk factors and prevent such memory dysfunction in patients after cardiac surgery as it has been found to have beneficial effects on the heart and brain.

Pomegranate

Epidemiological studies have suggested that consuming fruits and vegetables rich with polyphenols could have beneficial effects on health such as a reduced risk of cerebrovascular disease and cardiovascular disease (Hertog, Sweetnam, Fehily, Elwood & Kromhout, 1997a; Hertog, van Poppel & Verhoeven, 1997b) and a reduced risk of certain types of cancer (Heber, 2008). These polyphenols include epigallocatechin-3-gallate (found in green tea), curcumin (found in turmeric), resveratrol (found in red wine and grape juice), quercetin (found in grapefruit), and ellagic acid (found in raspberries

and pomegranates). Pomegranates are one of the dietary sources, highly rich in phenols compared to other fruits and vegetables, that has gained interest in recent years (Gil, Tomas-Barberan, Hess-Pierce, Holcroft & Kedar, 2000). The pomegranate, or *Punica granatum L.*, is a fruit that has been cultivated throughout the Mediterranean region, Himalayas, Southeast Asia, Iran, East Indies, Africa, California and Arizona. It has been used in the ancient times, believed to grant powers of fertility, wealth and luck. It has also been highly featured in the art, mythology and ceremonies of various cultures. Not only does the pomegranate have ancient historical purposes, but it has also been used to treat a range of ailments (Jurenka, 2008). For example, in Ayurvedic medicine, it has been used as an antiparasitic agent (Naqvi, Khan & Vohora, 1991) and as a remedy for diarrhea and ulcers (Lad & Frawley, 1986). Also, in the Unani system of medicine, practiced in the Middle East and India, the pomegranate has been used as a remedy for diabetes (Saxena & Vikram, 2004). More recently, however, it has been found to have antiatherogenic (protects against the formation of plaques in the arteries), antiproliferative (inhibition of cell growth), antioxidative (protects against the effects of free radicals) and anti-inflammatory (protects against inflammation) properties (Gil et al., 2000; Afaq, Saleem, Krueger, Reed & Mukhtar, 2005; Aviram & Dornfeld, 2001).

The pomegranate's anti-oxidative properties have been an important focus in recent years. Large amounts of dangerous oxidants or free radicals can affect DNA, lipids, proteins and carbohydrates causing the production of toxins, alteration of gene expression and enzyme activity, and the disruption of the repair process (Sies, 1997; Stanner, Hughes, Kelly & Buttriss, 2003). Oxidative stress (an imbalance between oxidants and antioxidants) has been shown to alter tissue structure and function in organs

such as the heart, blood vessels, lung, kidney, and brain (Azadzoi, Schulman, Aviram & Siroky, 2005) and is a metabolic trigger for inflammation and angiogenesis (formation of new blood vessels) which are key factors in the initiation and progression of cancer (Lansky et al., 2005; Lansky, Harrison, Froom & Jiang, 2005). Oxidative stress has also been implicated in the pathophysiology of many chronic diseases such as cardiovascular disease, diabetes (Stanner et al., 2003) and neurodegenerative disease (Smith et al., 1991; Marcus et al., 1998).

Biochemical Constituents in Pomegranate

Over the past decade, there has been considerable progress in finding the pharmacological mechanisms and constituents of the pomegranate responsible for its numerous health benefits. Pomegranate juice (PJ) contains 124 phytochemicals (also known as polyphenols) (Seeram, Schulman & Heber, 2006) such as tannins (punicalagins, ellagic acids, gallagic acids), which accounts for 92% of the antioxidant activity of the whole fruit (Malik, Afaq, Sarfaraz, Adhami, Syed & Mukhtar, 2005) and flavonoids (anthocyanins, catechins), which gives the fruit its red color (Sumner et al., 2005; Aviram & Dornfeld, 2001; Aviram et al., 2008; Syed, Afaq & Mukhtar, 2007; Malik, et al., 2005). The amount of soluble polyphenols in PJ ranges from 0.2-1.0% depending on the variety (Gil et al., 2000; Narr, Ayed & Metche, 1996).

One of the most potent and most researched polyphenols in pomegrantes is ellagic acid. Specifically, it has been shown to have powerful anti-cancer and antioxidant properties (Falsaperla, Morgia, Tartarone, Ardito & Romano, 2005; Losso, Bansode, Trappey, Bawadi & Truax, 2004; Hossoun, Vodhanel & Abushaban, 2004; Bohn, Forsyth, Stoner, Reed & Frank, 1998). Therefore, many commercial pomegranate

products have been standardized to contain 40% or more ellagic acid (Jurenka, 2008; Lansky & Newman, 2007). However, a prominent researcher on the medicinal properties of the pomegranate cautions against focusing on ellagic acid and overlooking the possible synergistic effects between ellagic acid and other pomegranate constituents (Lansky et al., 2005). Several studies have shown support for the synergistic effects of the various constituents, such as quercetin and reserveratrol (Mertens-Talcott, Bomser, Romero, Talcott & Percival, 2005; Mertens & Percival, 2005; Lansky et al., 2005; Lansky, et al., 2005), suggesting that there are more health benefits of a combination of constituents.

Variations between pomegranate accessions have also been explored. One study examined 29 accessions which differed in their peel and aril colors, taste and strength of seed shell. It was found that juices prepared from accessions that have a darker aril color have a higher antioxidant activity in comparison to accessions that have lighter arils. The results also showed that antioxidant levels are 2-fold higher in homogenates prepared from the whole fruit in comparison to homogenates prepared with arils alone (Tzulker et al., 2007).

Studies have also shown that the different parts of the pomegranate such as the aril, seed, juice, peel, leaf, flower, bark and roots all have therapeutic properties (Aviram et al., 2008; Naqvi et al., 1991). Aviram and colleagues analyzed the antiatherogenic properties of the various pomegranate parts in vivo and in vitro. They compared the peels, arils, seeds and flowers of the pomegranate to whole fruit juice which contains constituents from only the arils and outer peel. It was found that in atherosclerotic E° mice (created through gene targeting and and develop severe hypercholesterolemia) who

consumed pomegranate juice, peels, arils and flowers experienced a decrease in atherosclerotic lesions by 44, 39, 6 and 70% respectively (Aviram et al., 2008).

Safety of Pomegranate Extracts

Although pomegranates have proven to be beneficial, pharmacokinetic studies investigating pomegranate juice have implicated that there may be a concern for potential drug-food interactions. Pomegranate juice contains human cytochrome CYP450 enzyme inhibitory activity, similar to grapefruit juice which also has also been found to have adverse interactions with drugs (Summers, 2006). CYP450 is a human gene which catalyzes reactions involved in drug metabolism and synthesis of cholesterol, steroids, and other lipids leading to an excess of these drugs in the blood (Smith, Stubbins, Harries & Wolf, 1999). However, a recent in vitro study showed that grapefruit juice has greater inhibitory potency than pomegranate juice (Kim et al., 2006). In addition, many studies have demonstrated the safety of pomegranate juice intake. Studies have noted no toxic effects in animals after intake of pomegranate constituents at concentrations that were used in folk and traditional medicine (Vidal et al., 2003).

In a dose-response study, researchers investigated the potential adverse effects of pomegranate fruit extract (PFE) on rats. They administered 0, 60, 240, 600 mg/kg body weight/day of PFE for 90 days. Two additional groups received 0 and 600 mg/kg body weight/day of PFE for 90 days with a recovery period of 28 days. It was found that, compared to the controls, the intake of PFE did not result in any "toxicologically significant treatment-related changes" in clinical observations, ophthalmic examinations, body weight, organ weights, food consumption, and pathology evaluations (Patel, Dadhaniya, Hingorani & Soni, 2008). Cerd and colleagues (2003a) investigated the

effects of punicalagin (abundant in pomegranate) in Sprague-Dawley rats with repeated oral administration for 37 days. Results showed that there were no toxic effects or significant differences between the treatment and control groups. This was also confirmed through histopathological analysis of rat organs. More recently, for dietary supplement use, a pomegranate polyphenol extract, enriched in ellagitannin content, has been prepared using partially juice-pressed whole fruit, seeds and arils. This supplement, referred to as POMx, contains the same ellagitannins found in PJ, but does not contain the sugars and calories naturally found in the juice. One study examined the safety of this supplement and found that there were no adverse events following consumption of 1420 mg/day (2 capsules) of POMx (Heber et al., 2007).

Pomegranate Health Benefits

Heart

Early research conducted with pomegranates was primarily related to heart health, mostly in the area of atherosclerosis.

Atherosclerosis

Animal and human studies have examined the effects of pomegranate on the prevention and reduction of atherosclerosis. “Macrophage cholesterol accumulation and foam cell formation are the hallmarks of early atherosclerosis” (Ross, 1999). Kaplan and colleagues investigated the effect of pomegranate juice on macrophage lipid peroxidation, cellular cholesterol flux, and development of atherosclerotic lesions in applipoprotein E-deficient (E°) mice with advanced atherogenesis. Results showed that pomegranate juice significantly reduced macrophage lipid peroxidation, increased

cholesterol efflux by 39% compared to controls and reduced atherosclerotic lesion size by 17%. This suggests pomegranate effectively slowed down the progression of atherosclerosis (Kaplan et al., 2001).

A study by Rosenblat and colleagues investigated the effects of a pomegranate byproduct (PBP), which includes the whole pomegranate fruit left after juice preparation, on the development of atherosclerosis in apolipoprotein E-deficient (E°) mice. After the consumption of PBP, the mice had a significant reduction in atherosclerotic lesion size by up to 57%. Consumption of PBP also significantly reduced oxidative stress in the macrophages. In addition, oxidized low-level density lipoprotein uptake by the macrophages was reduced by 19%. The study concluded that PBP slows down atherosclerotic development due to its antioxidant properties (Rosenblat, Volkova, Coleman & Aviram, 2006).

In addition to atherosclerosis, the effects of pomegranate on other heart variables, such as myocardial perfusion (blood flow in the heart), has also been examined. Sumner and colleagues (2005) examined whether daily consumption of pomegranate juice for three months would affect myocardial perfusion (blood flow in the heart) in coronary heart disease and stress-induced ischemia (patients had undergone treadmill exercise or pharmacologic stress). The results showed that patients who consumed pomegranate juice daily (240ml/day) for three months had a decrease in stress-induced ischemia compared to the controls who had an increase in stress-induced ischemia. There was an average improvement of 17% in myocardial perfusion in the pomegranate juice group and an average worsening of 18% in myocardial perfusion in the control group.

Hypertension

There are many risk factors in the development of atherosclerosis. Hypertension is one of the known risk factors in the development of atherosclerosis. In addition, it has been shown to be a risk factor in valvular heart disease. Hypertensive patients with an elevated plasma-renin angiotensin activity have a five-fold increase risk of myocardial infarction. Angiotensin converting enzyme (ACE) inhibits the alteration of angiotensin I to angiotensin II which is a potent vasoconstrictor. Studies have shown that ACE inhibitors reduce mortality and morbidity in patients with myocardial infarction and ischemic events in patients with coronary artery disease. One study examined the effects of pomegranate juice consumption on blood pressure and on serum angiotensin converting enzyme of hypertensive patients. There was a 36% reduction in serum ACE activity and a 5% reduction in systolic blood pressure, suggesting that pomegranate juice has an inhibitory effect on serum ACE activity which can protect against the development of as well as progression of cardiovascular diseases (Aviram & Dornfeld, 2001).

Diabetes

Patients with type 1 or type 2 diabetes are at significant risk for coronary artery disease, valvular heart disease, stroke, and peripheral arterial disease. Atherosclerosis has been implicated in eighty percent of all deaths among diabetic patients. High blood sugar (hyperglycemia) reduces natural anti-oxidants and lends to the production of free radicals (Rosenblat et al., 2006). In addition, chronic episodes of high levels of blood glucose may directly affect insulin's action in the brain, damaging cells and causing cognitive

impairment (Society for Neuroscience, 2008). Insulin and its receptors are located in many parts of the brain. They are especially dense in the hippocampus, suggesting that diabetes may affect memory performance (Whitmer, 2007). One study investigated the effects of pomegranate flower (PGF) extract on hyperglycemia in Zucker diabetic fatty (ZDF) rats. Results showed that PGF inhibited the increase of plasma glucose levels in glucose-loaded ZDF rats, but had no effect on fasted ZDF rats. PGF also did not lower glucose levels in fasted or glucose-loaded Zucker lean (ZL) rats. These results indicated that PGF lowers glucose levels by improving the sensitivity of insulin receptors rather than promoting secretion of insulin or inhibiting the absorption of glucose (Huang et al., 2005).

Brain

"Brain aging is characterized by the continual concession to battle against insults accumulated over the years" (Lau, Bielinski & Joseph, 2007). One of the key insults is oxidative stress. Not only has it been implicated in the aging process, but also in several diseases including cerebrovascular and neurodegenerative diseases (Cherubini et al., 2008). In normal aging, cognitive declines result as the brain undergoes morphological and functional changes. In neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, these cognitive declines are amplified (Lau et al., 2007).

Alzheimer's Disease

Although very few studies have examined the effects of pomegranate juice on the brain, the limited research shows some promising results, especially in the areas of Alzheimer's and Parkinson's disease. Research suggests that diet can affect the risk for

Alzheimer's disease (AD) and modify amyloid-β levels (Aβ) which has been found to be the main constituent of the plaques that are deposited in the brains of AD individuals. Studies have shown that antioxidant-rich foods may prevent or neutralize the damaging effects of free radicals, thereby slowing down the progression of AD (Kostrzewa and Segura-Aguilar,2003; Polidori, 2003). One study examined whether dietary supplementation with pomegranate juice would affect AD-like pathology and behavior in mice. It was found that the PJ-treated mice learned water maze tasks more quickly and swam faster than the controls. They also had 50% less accumulation of beta-amyloid and plaque load in the hippocampus compared to the mice that received sugar water, suggesting that PJ may be neuroprotective (Hartman et al., 2006). Moreover, research has demonstrated that hypoxia and reduced blood supply increase the levels of free radicals and the amount of beta-amyloid in the brain (Peers et al., 2009). Therefore, it can be implicated that pomegranate may have a beneficial effect on the brain and cognitive function by way of lessening damage secondary to hypoxia and reduction of beta-amyloid.

Neonatal Hypoxic-Ischemic Brain Injury

Other studies have investigated the effects of pomegranate juice on neonatal hypoxic-ischemic brain injury in severely preterm and low birth weight babies. This type of injury can lead to encephalopathy, seizures, permanent motor impairment, and death (Hankins & Speer, 2003; Shevell, 2004; Volpe, 2001; Back, 2001). Two studies examined whether supplementing the maternal diet with pomegranate juice would protect the neonatal mouse brain from a experimentally induced hypoxic-ischemic insult when

compared to pregnant mice that consumed a control beverage. Results showed that there was significantly less brain tissue loss (64% decrease) and significantly less hippocampal caspase-3 activity (84% decrease) compared to the controls. These results demonstrated that pomegranate juice may have an "antioxidant-driven neuroprotective effect" given from the mother to the neonate (Loren, Seeram, Schulman & Holtzman, 2005; West, Atzeva & Holtzman, 2007). In addition, these results illustrate pomegranate's potential ability to protect against hypoxia. As mentioned previously, hypoxia and ischemia have been found to be potential causes of cognitive dysfunction after cardiac surgery. Therefore, it may be speculated that pomegranate will reduce hypoxia and ischemia, and subsequently, protect against cognitive decline postsurgically.

Cognition

Although no studies have examined the effects of pomegranate juice on cognitive functioning in humans, there have been significant findings showing the beneficial effects of the polyphenols found in other fruits and berries (which have similar polyphenols as in pomegranates) on cognitive functioning. Flavonoids are the most common type and most studied of the polyphenols found in the human diet and can be found in fruits, vegetables, cereals, tea, wine and fruit juices (Spencer, 2008). Although polyphenols were initially explored for their antioxidant activity, there is evidence suggesting that they exhibit an array of effects on the brain. Polyphenols from berry supplementation have not only been shown to decrease oxidative stress, but have also been found to stimulate changes in gene expression and signaling activity (Willis, Shukitt-Hale & Joseph, 2009). In one study, it was found that blueberry supplementation after hippocampal damage by a neurotoxin led to an increase in the number of neurons surviving damage and also reduced the number

of activated microglia and expression of proinflammatory cytokines in the hippocampus. This suggests that the buildup of oxidative species may lead to alterations in microglia activation and cytokine expression which may reduce the damage of the neural tissue of the hippocampus (Shukitt-Hale et al., 2008). One study demonstrated that polyphenols can directly affect microglia activation, leading to a decrease in the amount of cytotoxins released by cells (Lau et al., 2007). Specifically, flavonoids have been shown to have the ability to interact with a number of neuronal proteins and signaling pathways that assist in synapse growth, increase in the density of dendritic spines, and increased membrane receptor density, all of which have been associated with the acquisition, consolidation and storage of memory (Spencer, 2008). Therefore, flavonoids may improve memory functioning.

Papandreou & colleagues examined the effects of a polyphenol-rich extract of blueberries (which contain anthocyanins) on a test of learning and memory in adult *Balb-c* mice for 7 days by intraperitoneal administration. Results showed that there was significant improvement in learning and memory compared to the control group (Papandreou et al., 2008). Another similar study found that not only do flavonoids enhance the animal's spatial memory, but the improvement in memory is associated with increased neurogenesis and neuronal spine density in the dentate gyrus of the hippocampus, as well as with the up-regulation of genes that are associated with learning and memory (van Praag et al., 2007).). The potential cognitive benefits of flavonoid intake were further illustrated in a prospective study of flavonoid intake and cognitive decline in 1,640 dementia-free subjects over a ten-year period. It was found that subjects in the two higher quartiles of flavonoid intake had better cognitive performance than

those individuals in the lower quartile of flavonoid intake. Ten-year follow up revealed that subjects with the lowest flavonoid intake lost an average of 2.1 points on the Mini-Mental Status Exam (MMSE) and subjects in the higher quartiles lost an average of only 1.2 points on the MMSE (Letteneur, Proust-Lima, Gouge, Dartigues & Barberger-Gateau, 2007).

There is empirical support that the phytochemicals found in fruits can cross the blood-brain barrier and localize in various parts of the brain. These regions may therefore be affected by phytochemicals which may in turn translate to various cognitive/behavioral changes. One study examined whether different polyphenols could be found in different areas of the brain following blueberry supplementation in aged rats. Several anthocyanins were found most frequently in the hippocampus and cortex in the blueberry supplementation group, but similar concentrations were not found in the controls supporting the hypothesis that indeed certain polyphenols cross the blood-brain barrier and localize in certain areas of the brain. They also found a relationship between Morris Water Maze performance (which measures spatial learning and memory) and the total number of anthocyanins found in the hippocampus and cortex (Andres-Laceuva et al., 2005) suggesting anthocyanins concentration in the hippocampus may directly impact learning and memory.

In sum, research has revealed that the polyphenols found in pomegranates have been beneficial to health and more specifically, to the brain. There is evidence that polyphenols in pomegranates prevent or reduce the incidence of certain diseases, as well as target some of the factors associated with cardiac surgery and cognitive declines (i.e., ischemia, hypoxia, oxidative stress). Studies have also demonstrated that these powerful

polyphenols cross the blood-brain-barrier and affect certain regions of the brain such as the hippocampus, an important area for learning and memory.

Given the research findings from cardiac surgery and pomegranate studies, it is plausible to hypothesize that the consumption of pomegranate may benefit CABG and heart valve surgery patients experiencing these declines, specifically in the realm of memory.

Aims and Hypotheses

Aim 1

The first aim of the current study is to examine the impact of pomegranate supplementation on memory performance after cardiac surgery. This will be examined by comparing composite memory scores of a treatment group to the placebo group across three testing time points. Composite memory scores will include learning, immediate memory, delayed memory, retention and recognition.

Hypothesis 1

There will be a greater reduction in each composite memory score across time for the placebo group compared to the treatment group.

Aim 2

The second aim of this study is to examine the impact of pomegranate on the incidence of significant changes in memory performance after cardiac surgery. More

specifically, identify the incidence of memory impairment and comparing the incidence of memory impairment across groups.

Hypothesis 2

The placebo group will have a greater number of individuals with clinically significant declines in memory performance, while the treatment group will have a greater number of individuals with clinically significant improvements in memory scores.

Conclusions

Heart disease is the leading cause of death in the U.S. and has been shown to be associated with cognitive declines. Coronary artery bypass grafting and heart valve surgery have been employed as treatments to help restore cardiac functioning at an optimal level. Although CABG and heart valve surgery have decreased mortality rates associated with heart disease, there is evidence of cognitive declines early in the postoperative period with some evidence of declines in the late postoperative period. One of the cognitive functions consistently reported and objectively shown to decline after cardiac surgery is memory (Kesner & Hopkins, 2006). Research on cardiac surgery has shown objective, subjective, imaging and histological evidence that memory is impacted after cardiac surgery with specific implications of damage to the hippocampus. The mechanisms for memory dysfunction may be linked to the pathophysiology of heart disease itself, the surgical procedures often used to treat the heart disease, or even individual differences of those with heart disease. Nutritional supplements have been proven successful in moderating some of these heart disease risk factors, and thus it is speculated that they may thereby moderate the negative cognitive consequences of heart

disease and surgical interventions as well. Since the ancient times, the pomegranate has been shown to have beneficial effects on health. Various studies have suggested that the consumption of polyphenols contained in fruits (such as pomegranates) and vegetables may target areas of the brain that are important in learning and memory, such as the hippocampus.

Preventive options for the cognitive declines observed after cardiac surgery have not been examined extensively. Given the vast literature on the beneficial effects of pomegranate on a wide variety of heart and brain functions, this study will aim to understand and examine the effects of pomegranate supplementation on memory dysfunction after cardiac surgery.

CHLAPTER TWO

MATERIALS AND METHODS

Participants

Ten elective cardiac surgery patients (CABG and/or valve repair/replacement) who met eligibility criteria and signed a written informed consent participated in this study. Participants had at least six years of education (to assure the appropriate use of the standardized neuropsychological tests). They were recruited from the Loma Linda University International Heart Institute at the time they presented for a preoperative evaluation and scheduled surgery. Participants who had a history of previous cardiac surgery, planned concomitant non-coronary procedures, history of allergy to pomegranates, history of head injury, neurodegenerative disease or neurologic condition with known cognitive impact (e.g., Alzheimer's disease, Muscular Sclerosis), history of drug or alcohol abuse, psychiatric disorder (according to DSM-IV diagnostic criteria), active renal disease (indicated by a serum creatinine concentration higher than 2.0 mg per deciliter), active liver disease, or left ventricular ejection fraction of less than 20% were excluded from the study. In order to assure equal sample sizes between groups for the initial group of pilot data, patients were alternated to either treatment of placebo group.

Administration of Study Supplement

Participants in the treatment group were given two pomegranate (PomX) capsules (one capsule in the morning and one in the evening). Each of these capsules contained 1000mg of concentrated extract. Participants in the placebo group were given two placebo capsules (one capsule in the morning and one in the evening). These capsules

were taken daily starting one week before surgery (when possible, though scheduling and recruitment limitations resulted in some subjects starting the supplement between 2 and 6 days prior to surgery) and continued to 6 weeks after surgery.

Neuropsychological Assessments

A comprehensive battery of cognitive tests was administered three times during the course of each patient's participation. These tests were administered just prior to the first pomegranate pill administration (approximately one week before surgery), two weeks after surgery, and 6 weeks after surgery. Trained graduate students in psychology, or the licensed clinical psychologist associated with this study performed all cognitive assessments under standardized conditions. All examiners and patients were blinded to treatment group.

All subjects were administered a comprehensive battery of neuropsychological tests at each testing session. For the purpose of this study, those tests assessing memory functions were selected. The selected measures included the Wechsler Adult Intelligence Scale – III (WAIS-III; Digit Span subtest), Hopkins Verbal Learning Test – Revised (HVLT-R), Wechsler Memory Scale - III (WMS-III; Logical Memory subtest), and Rey Complex Figure Test (RCFT) with Recognition (using the Meyers and Meyers scoring system). Alternate forms of the HVLT-R are available, and were administered using a randomization code. Shortly after initiation of the study, the RCFT (which does not have alternate forms) was replaced by the Brief Visuospatial Memory Test (BVMT) (which does have alternate forms) in order to reduce potential practice effects. Alternate forms of the BVMT were administered according to a randomization code. Additionally, the

Logical Memory subtest, which has no alternate forms nor acceptable replacements, was changed from being administered three times (time 1, time 2 and time 3) to two times (time 1 and time 3) in order to reduce potential practice effects.

Information was gathered on a number of biomedical risk factors and demographic variables, including prior history of smoking, hypertension, cholesterol, diabetes, education, and social support. An IQ estimate was calculated using the sum of scaled scores from WAIS-III Vocabulary and Matrix Reasoning subtests (ERSET operations manual).

Statistical Analyses

Analyses were carried out using the SPSS (PASW Statistics 18) statistical software package (SPSS, Inc., Chicago, IL).

Demographic Group Differences

Group differences on demographics were examined with independent samples t-tests for continuous data and chi-square (X^2) tests for categorical data.

Memory Scores

In order to examine differences between the groups on memory dysfunction (hypothesis 1), each patient's raw scores on the selected memory test variables were converted into z-scores using normative data (taking into account age and educational level). Composite scores were created for each component of memory function, such as immediate memory, delayed memory, and retention by summing the z-scores and dividing each sum by the number of tests administered for that subject within each

domain. Learning and recognition scores, however, were created only using one score from one memory test (Hopkins Verbal Learning Test-Revised) as this was the one measure that was consistently administered to all the patients that yielded a learning score and that included a recognition format.

Between and Within Group Differences

A repeated measures analysis of variance (ANOVA) was conducted to examine the differences between and within the groups on each of the components of memory. For this analysis, group membership (treatment versus placebo) served as the between-subjects variable, and time (baseline, 2 week post-op and 6 week-post op) served as the within-subjects (repeated measures) variable. Paired-samples t-tests were conducted from time 1 to time 2, time 2 to time 3, and time 1 to time 3 for each composite measure for both treatment and placebo groups in order to examine significant memory changes for each specific time period.

Effect Size and Power

Given the small sample size, effect sizes were calculated using Cohen's d statistics and power analysis was conducted using the software program called G*Power.

Post-hoc Analyses

Post-hoc analyses included paired-samples t-tests which were conducted from time 1 to time 2, time 2 to time 3, and time 1 to time 3 for each individual measure for both treatment and placebo groups in order to examine significant memory changes for each time period.

The incidence of memory impairment or improvement (hypothesis 2) was examined using each of the composite scores of memory. A change z-score was calculated from preoperative (baseline) to 2 week postoperative, from 2 week postoperative to 6 week postoperative, and from preoperative to 6 week postoperative. Scores that were one standard deviation below or above each individual's own preoperative z-score were considered an impairment or improvement, respectively (Kneebone, Andrew, Baker & Knight, 1998). Furthermore, these calculations were performed for each individual memory test. In order to examine whether any change between time points was attributable to true, clinically significant change rather than simply measurement unreliability and practice effects from repeated administration of tests, reliable change indices were calculated for each memory measure based on formulations from Chelune and colleagues (1993) that took into account quantified practice effects and test-retest reliability. This formulation allows you to determine who has changed reliably (i.e., more than the unreliability of the measure would suggest might happen for 95% of subjects) by seeing if the difference between the follow-up and initial scores is more than a certain level. These indices were only calculated for time 1 to time 2 as normative data (means, sd, test-retest reliability) were not available for multiple testings beyond two. The reliable change index calculations require use of raw scores for each patient on each individual measure at each time point, means and standard deviations from a normative population on that measure at each time point, and the test-retest reliability coefficient. A cut-off (z-) score for significant change ("impairment" if the change is in the negative direction, "improvement" if the change is in the positive direction) using the reliable change index is most typically set at +/-1.65 standard

deviations, as changes greater than this represents more change than might otherwise be expected due to the simply unreliability of the measure with repeated administration to the same individual. In the absence of appropriate normative data for evaluating reliable change from time 2 to time 3, a significant decline/improvement from time 2 to time 3 was defined as a change of 1.65 or more standard deviations below or above the mean raw score for that measure for the entire sample.

Additionally, outlier analyses were conducted when applicable. A z-score of +/- 3 standard deviations from the mean was considered to be an outlier.

Operational Definitions

Independent Variable

Time: Neuropsychological tests were conducted on each participant one week before surgery, two weeks after surgery and six weeks after surgery.

Dependent Variables: Tests of Memory Functioning

Hopkins Verbal Learning Test – Revised (HVLT-R)

This test is a list-learning task that assesses verbal learning and memory and consists of three immediate recall trials, a 20 minute delayed recall trial and a recognition trial consisting of 12 words. There is an immediate recall score (total of all three trials), learning score (highest of T2 or T3 minus T1), delayed memory score which is the total number of words recalled after the delay, and a recognition score which is the total number of words recalled in a list of target words and distractors (Benedict, Schretlen, Groninger & Brandt, 1998). A retention score representing the percentage of information

retained was created using the following formula: {[(learning score – delayed recall score) / learning score] x 100} – 100

Rey Complex Figure Test with Recognition Trial (RCFT)

This test assesses visuospatial memory and consists of a copy trial, an immediate recall trial (3 minutes), a delayed recall trial (30 minutes), and a recognition trial. Scores include a copy score (which reflects the accuracy of the original figure and the time required to copy the figure), immediate and delayed recall scores (assesses the amount of information retained over time) and the number of items correctly and incorrectly identified on a recognition task (Rey, 1941; Osterrieth, 1944). A retention score representing the percentage of information retained was calculated using the following formula: {[(learning score – delayed recall score) / learning score] x 100} – 100.

Logical Memory Subtest of Wechsler Memory Scales

This test assesses contextual verbal learning and memory and consists of two stories that are read out loud by the examiner. The first story is read once and the second story is read twice. Participants are to recall the stories immediately and after a 25-35 minute delay and are given a yes/no recognition trial following the delays. Scores include an immediate recall and delayed recall (reflecting the amount of information retained over time) for all the details of both stories, learning score for the second story, and a recognition score (Wechsler, 1945). A retention score representing the percentage of information retained was created using the following formula: {[(learning score – delayed recall score) / learning score] x 100} – 100.

Brief Visuospatial Memory Test – Revised (BVMT-R)

This test assesses visuospatial memory and consists of three trials in which a display of 6 figures is presented for 10 seconds and participants are required to draw the figures in their correct locations on the page after each trial. They are required to recall these figures after a 20 minute delay and are given a yes/no recognition trial following the delays. Scores include immediate recall (total of all trials), delayed recall, learning and a recognition score (Benedict, Schretlen, Groninger, Dobraski, & Sphritz, 1996). A retention score representing the percentage of information retained was created using the following formula: {[(learning score – delayed recall score) / learning score] x 100} – 100.

CHAPTER THREE

RESULTS

Demographics

The placebo group consisted of Caucasians (60%), Asians (20%), and Hispanics (20%) with 60% being males and 40% females. The mean age of the placebo group was approximately 70.2 years, the mean number of years of education was 15 years and the mean IQ estimate was 106.6. There was a high percentage of individuals with a history of high cholesterol (75%) and smoking history (80%). Percentage of individuals with hypertension and diabetes were 40% and 20%, respectively (see Table 1). The treatment group consisted of Caucasians (60%), Asians (20%), and Hispanics (20%) (all males). The mean age of this group was approximately 62.4 years. The mean number of years of education was 15.3 years and the mean estimated IQ was 100.6. Of note, there was a participant with an IQ estimate of 71. This individual was examined as a possible outlier (approaching the 3 standard deviations cut-off used) given his low IQ score. It appeared as though his IQ estimate may have been pulled down by a low vocabulary score. However, upon closer examination of his scores, all individual measures compared in this study revealed that his scores were all within the acceptable range of variability. That is, none of his scores were more than 3 standard deviations from the mean. Therefore, this individual was not excluded from the study. There was a high percentage of individuals with a history of hypertension (100%), high cholesterol (100%) and smoking history (80%). Percentage of individuals with diabetes was 60% (see Table 2). There were no significant differences between groups on demographic factors such as age, education

and estimated IQ. Additionally, there were no significant differences between groups on medical factors, such as cholesterol (p=.24), diabetes (p=.29) and hypertension (p=.07).

Table 1

Demographics – Means and Percentages of the Placebo Group

	Mean (s.d.)	%
PLACEBO		
Age (yrs)	70.2 (8.11)	
Education (yrs)	15.0 (2.0)	
IQ estimate	106.6 (14.43)	
Gender (%)		
Male		60.0
Female		40.0
Ethncity (%)		
Caucasian		60.0
Hispanic		20.0
Asian		20.0
Marital Status		
Married		100.0
Single		0.0
Divorced		0.0
Widowed		0.0
Diabetes		20.0
Hx of high cholesterol		75.0
Hx of hypertension		40.0
Hx of smoking		0.0
Surgery type		
CABG		60.0
Valve Repair		20.0
Valve Repair & Replacement		20.0

Table 2

Demographics – Means and Percentages of the Treatment Group

	Mean (s.d.)	%
TREATMENT		
Age (yrs)	62.4 (8.6)	
Education (yrs)	15.3 (2.2)	
IQ estimate	100.6 (20.5)	
Gender (%)		
Male		100.0
Female		0.0
Ethncity (%)		
Caucasian		60.0
Hispanic		20.0
Asian		20.0
Marital Status		
Married		60.0
Single		0.0
Divorced		20.0
Widowed		0.0
Diabetes		60.0
Hx of high cholesterol		100.0
Hx of hypertension		100.0
Hx of smoking		80.0
Surgery type		
CABG		60.0
Valve Replacement & CABG		40.0

Between and Within Group Comparisons

A repeated-measures analysis of variance (ANOVAs) was conducted using the pre-surgery, two week post-surgery and six week post-surgery composite memory scores (immediate memory, delayed memory, learning, retention, and recognition) in order to examine differences between and within groups at each time point. ANOVA results for

immediate memory showed no significant difference within groups [F(2,16) = 1.807, p=.196], between groups [F(1, 8) = .055, p=.821], and no interaction [F(2,16) = .579, p=.572] (see Table 3). ANOVA results for delayed memory showed no significant difference within groups; however, the difference was approaching a significant level [F(2, 14) = 2.947, p=.085]. There was no significant difference between groups [F(1,7) = .002, p=.966] and no interaction [F(2,14) = .753, p=.489] (see Table 4). ANOVA results

Table 3

Analysis of Variance for Composite Immediate Memory pre-surgery, 2 weeks post-surgery, and 6 weeks post-surgery

Source	SS	df	MS	F	p	Partial Eta Squared
Within-Subjects						
Immediate Memory	.588	2	.294	1.807	.196	0.184
Immediate*Group	.188	2	.094	.579	.572	.067
Error	2.606	16	.163			
Between-Subjects						
Intercept	.633	1	.633	.244	.635	.030
Group	.142	1	.142	.055	.821	.007

Table 4

Analysis of Variance for Composite Delayed Memory pre-surgery, 2 weeks post-surgery, and 6 weeks post-surgery

Source	SS	df	MS	F	p	Partial Eta Squared
Within-Subjects						
Delayed Memory	.845	2	.422	2.947	.085	.296
Delayed*Group	.216	2	.108	.753	.489	.097
Error	2.007	14	.143			
Between-Subjects						
Intercept	.023	1	.023	.005	.944	.001
Group	.008	1	.008	.002	.966	.000

for learning showed no significant difference within groups [F(2,14) = .425, p=.662), no significant difference between groups [F(1,7) = .513, p=.497], and no interaction [(F(2, 14) = .969, p =.404] (see Table 5). ANOVA results for retention showed no significant difference within groups [F(2,14) = .086, p=.918], no significant difference between groups [F(1,7) = 1.793, p=.222] and no interaction [F(2,14) = .860, p = .444] (see Table 6). ANOVA results for recognition showed no significant differences within groups [F(2,16) = 1.05, p=.373], no significant difference between groups [F(1,8) = .686, p = .432], and no interaction [F(2,16) = .332, p=.723] (see Table 7).

Table 5

Analysis of Variance for HVLT learning pre-surgery, 2 weeks post-surgery, and 6 weeks post-surgery

Source	SS	df	MS	F	p	Partial Eta Squared
Within-Subjects						
Learning	.349	2	.175	.425	.662	.057
Learning*Group	.796	2	.398	.969	.404	.122
Error	5.75	14	.411			
Between-Subjects						
Intercept	.023	1	.023	.014	.909	.002
Group	.832	1	.832	.513	.497	.068

Table 6

Analysis of Variance for Composite Retention pre-surgery, 2 weeks post-surgery, and 6 weeks post-surgery

Source	SS	df	MS	F	p	Partial Eta Squared
Within-Subjects						
Retention	18.384	2	9.192	.086	.918	.012
Retention*Group	183.096	2	91.548	.860	.444	.109
Error	1489.541	14	106.396			
Between-Subjects						
Intercept	186649.798	1	186649.798	258.181	.000	.974
Group	1295.904	1	1295.904	1.793	.222	.204

Table 7

Analysis of Variance for Composite Recognition pre-surgery, 2 weeks post-surgery, and 6 weeks post-surgery

Source	SS	df	MS	F	p	Partial Eta Squared
Within-Subjects						
Recognition	1.413	2	.706	1.05	.373	.116
Recognition*Group	.446	2	.223	.332	.723	.04
Error	10.76	16	.673			
Between-Subjects						
Intercept	1.240	1	1.240	.389	.550	.046
Group	2.187	1	2.187	.686	.432	.079

Paired samples t-tests of each composite memory measure from time 1 to time 2, time 2 to time 3, and time 1 to time 3 revealed no significant declines/improvements on any composite memory measure for the placebo group. However, an improvement in delayed memory for the treatment group from time 1 to time 3 approached significance [$t(4) = -2.762$, $p=.05$].

Effect Sizes and Power

Effect sizes, power and required sample size were calculated for composite measures at each time point (see Table 8). Effect sizes for immediate memory ranged from medium to negligible over time. Delayed memory effect sizes were small and did not change over time. Effect sizes for learning ranged from medium to small over time. Recognition effect sizes ranged from large to small over time. Retention effect sizes ranged from small to very large over time.

Table 8

Effect Sizes and Power for Composite Memory Measures

	n (control)	n (treatment)	Control mean	Control sd	Treatment mean	Treatment sd	Effect size	Power	Required n
T1 Immediate Memory	5	5	-.1360	.82827	-.4933	.83605	.48 (Medium)	.2986	52
T2 Immediate Memory	5	5	-.1547	.80500	-.1440	1.01686	.01 (Negligible)	.0501	--
T3 Immediate Memory	5	5	.0613	.91806	-.0047	1.38836	.06 (Negligible)	.0537	--
T1 Delayed Memory	5	5	-.0520	1.11604	-.3527	.92152	.33 (Small)	.1630	110
T2 Delayed Memory	5	4	-0.274	1.17581	-0.0408	1.44091	.2 (Small)	.0906	296
T3 Delayed Memory	5	5	.1847	1.28965	.3633	1.18944	.16 (Small)	.0759	466
T1 Learning	5	5	-.332	1.203	.3900	.96225	.74 (Medium)	.651	22
T2 Learning	4	5	-.334	1.07	.1125	.78725	.55 (Medium)	.371	36
T3 Learning	5	5	.224	.46495	.115	.64086	.22 (Small)	.128	180
T1 Retention	5	5	79.9200	16.22869	83.0733	10.19925	.26 (Small)	.1265	160
T2 Retention	5	4	74.5867	26.02112	91.2917	11.85591	.92 (Large)	.9028	16
T3 Retention	5	5	75.5667	21.07795	93.6	10.20185	1.22 (Very Large)	.9599	10
T1 Recognition	5	5	.40	.53385	-.4800	1.486	.88 (Large)	.8559	14
T2 Recognition	5	5	.10	.74162	-.2200	1.04259	.40 (Medium)	.2843	56
T3 Recognition	5	5	-.30	1.56045	-.7200	1.58335	.30 (Small)	.1448	74

Post-hoc Analyses

Although there are limited significant ANOVA and paired samples t-tests results, patterns in the illustrations of the composite memory scores suggest otherwise. For example, Figure 1 illustrates the composite scores for immediate memory at each time point. It is observed that at time 2, there is a sharp improvement compared to pre-operative scores for the treatment group, but not for the placebo group (the placebo group remains relatively stable). However, by time 3, both groups improve and perform similarly. Figure 2 illustrates the composite scores for delayed memory at each time point. There is an improvement observed for the treatment group at time 2 compared to baseline; however, the placebo group shows a decline from baseline at time 2. Similar to immediate memory, both groups improve at time 3 and ultimately perform at a similar level. On the other hand, Figure 3 reveals a different pattern for learning. The treatment

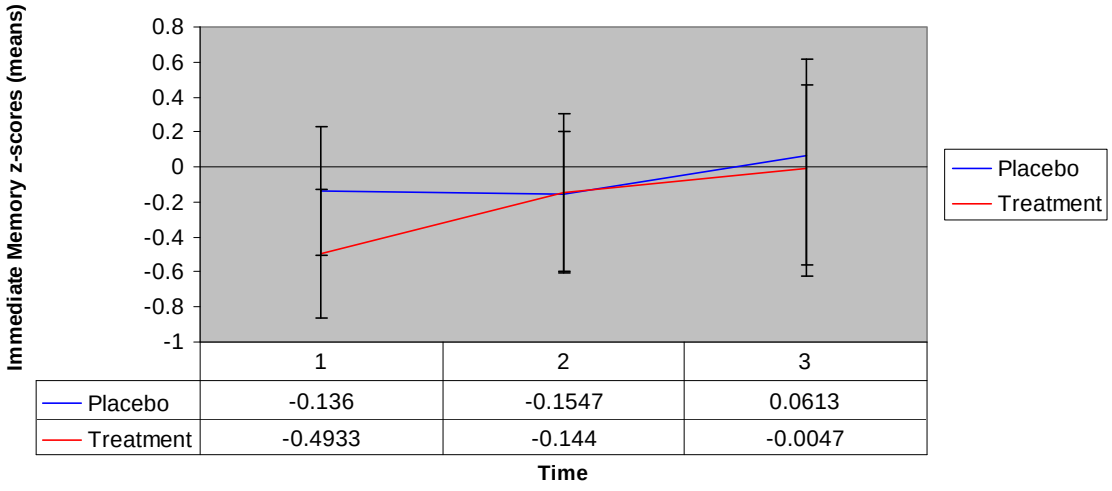


Figure 1. Performance on immediate memory (composite) for placebo and treatment groups

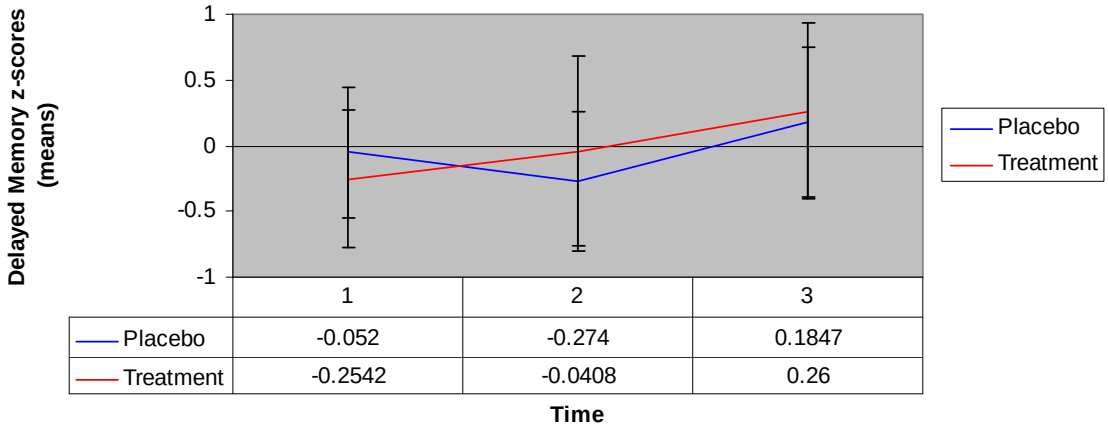


Figure 2. Performance on delayed memory (composite) for placebo and treatment groups

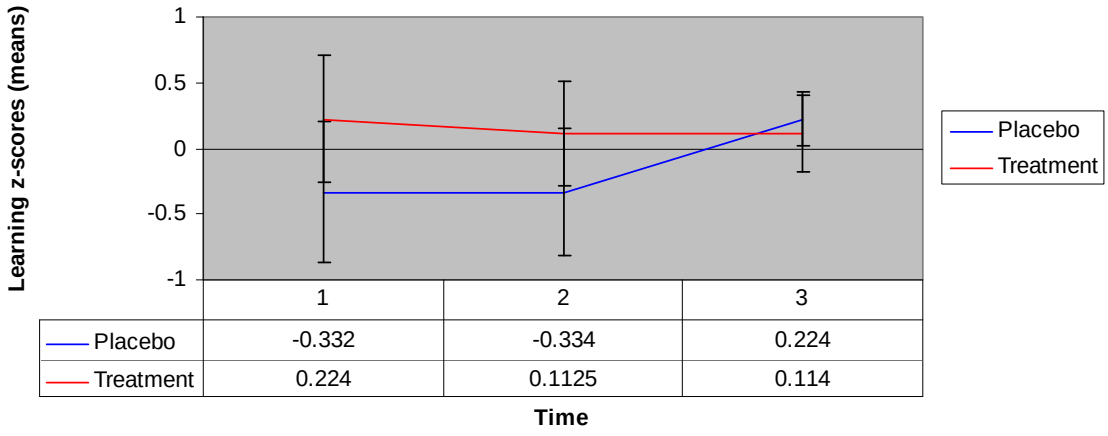


Figure 3. Performance on learning (HVLT-R) for placebo and treatment groups

group declines by time 2, but the placebo group remains relatively stable. Additionally, by time 3, the placebo group shows a sharp improvement, while the treatment group shows little improvement. Figure 4 illustrates the composite scores for retention at each time point. It is observed that at time 2, there is an improvement for the treatment group and a decline for the placebo group. Both groups improve at time 3. Figure 5 reveals a

different pattern for recognition. By time 2, the treatment group improves and the placebo group declines; however, at time 3 both groups decline sharply.

Paired samples t-tests were conducted for treatment and placebo groups on each individual test at each time point to highlight more clearly the nature of deficits after cardiac surgery. Although the Bonferroni correction was not applied, it is important to note near significance levels.

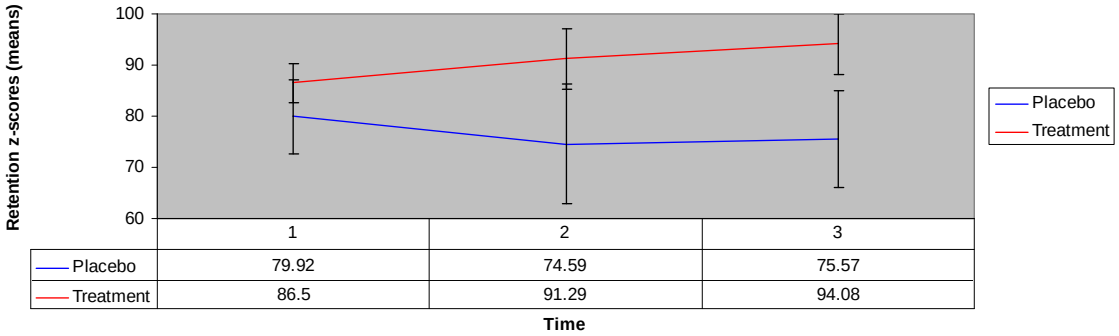


Figure 4. Performance on retention (composite) for placebo and treatment groups

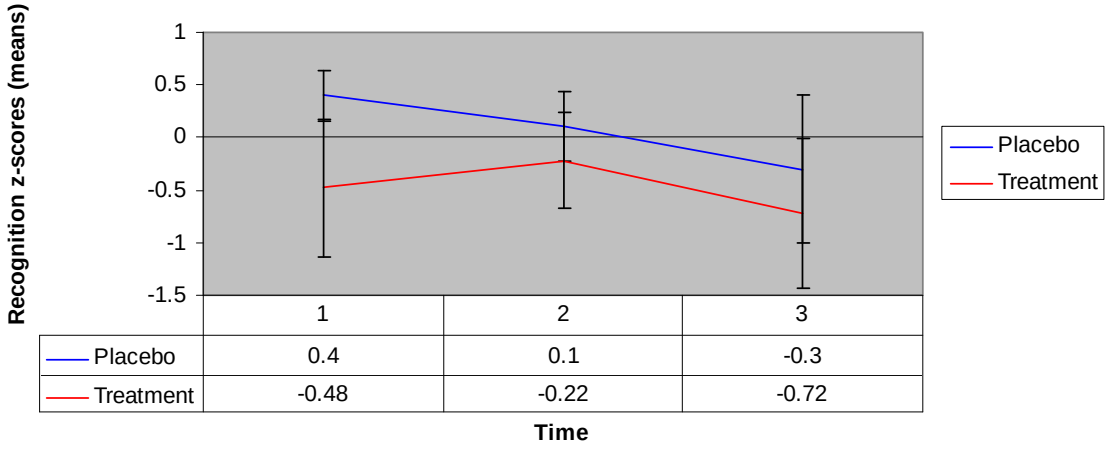


Figure 5. Performance on recognition (HVLT-R) for placebo and treatment groups

Logical Memory

For the placebo group, there were no significant differences between time 1 to time 2 or time 2 to time 3 on any of the Logical Memory variables (see Tables 9 and 10). However, a near significant level was reached from time 1 to time 3 for immediate memory [t(4) = -3.87, p=.02], delayed memory [t(3) = -5.0, p=.02], and retention [t(3) = --5.98, p = .01] (see Table 11), with better performances at time 3 compared to time 1. For the treatment group, a near significant change was reached from time 1 to time 2 for immediate memory [t(2) = -3.67, p=.07] (see Table 12), time 2 to time 3 for retention [t(2) = -5.96, p=.03] (see Table 13), and time 1 to time 3 for retention [t(4) = -2.69, p=.06] (see Table 14), with better performances at the latter time points.

Table 9

Paired T-Tests of Individual Measures at t1 and t2 for the Placebo Group

	Pre-surgery raw scores		2 week post-surgery raw scores			
	Mean	Sd	Mean	Sd	t	p
Logical Memory						
Immediate Memory	38.5	7.8	51.5	12.0	-4.33	.144
Delayed Memory	23.5	3.5	27.5	3.5	-.800	.570
Learning	4.5	2.1	1.5	2.1	--	--
Retention	82.8	24.3	77.8	4.0	.347	.787
Hopkins Verbal Learning Test						
Immediate Memory	24.4	5.81	22.4	5.13	.784	.477
Delayed Memory	8.2	3.42	7.2	4.55	1.20	.298
Learning	3.2	2.17	3.2	1.92	.000	1
Retention	82.2	15.03	65.8	31.9	.489	.651
Recognition	11.4	.894	10.8	1.30	1	.374
Rey-Osterrieth Complex Figure Test						
Immediate Memory	16.5	14.14	15.0	19.1	.429	.742
Delayed Memory	15.5	16.97	15.25	17.32	1.0	.50
Retention	46.15	42.21	47.7	41.72	-3.08	.20
Recognition	18.5	.71	20.0	2.83	-1.0	.50
Brief Visuospatial Memory Test						
Immediate Memory	11.67	6.51	17.0	7.81	-2.44	.135
Delayed Memory	5.67	2.52	6.67	2.08	-1.73	.225
Learning	3.33	1.53	5.0	2.0	-1.39	.30
Retention	100.0	0	85.67	12.9	1.925	.194

Table 10

Paired T-Tests of Individual Measures at t2 and t3 for the Placebo Group

	2 week post-surgery raw scores		6 week post-surgery raw scores			
	Mean	Sd	Mean	Sd	t	p
Logical Memory						
Immediate Memory	51.5	12.02	49.5	2.12	.286	.823
Delayed Memory	30	--	34	--	--	--
Learning	1.5	2.12	2.5	4.95	-.200	.874
Retention	75	--	92	--	--	--
Hopkins Verbal Learning Test						
Immediate Memory	22.4	5.13	22	5.43	.279	.794
Delayed Memory	7.2	4.55	6.6	3.65	.885	.426
Learning	3.2	1.9	4.2	.84	-1.29	.266
Retention	75.6	43.8	65.8	31.9	1.31	.260
Recognition	10.8	1.3	10.6	1.67	3.03	.854
Rey-Osterrieth Complex Figure Test						
Immediate Memory	15.0	19.09	12.25	13.08	.647	.634
Delayed Memory	15.25	17.32	14.25	15.91	1.0	.50
Retention	49.85	43.91	47.7	41.72	1.387	.398
Recognition	20.0	2.83	19.0	2.83	--	--
Brief Visuospatial Memory Test						
Immediate Memory	17.0	7.81	16.67	8.96	.378	.742
Delayed Memory	6.67	2.08	7.0	4.58	-.189	.868
Learning	5.0	2.0	4.67	2.89	.164	.885
Retention	85.67	12.9	86.67	23.09	-.105	.926

Table 11

Paired T-Tests of Individual Measures at t1 and t3 for the Placebo Group

	Pre-surgery raw scores		6 week post-surgery raw scores			
	Mean	Sd	Mean	Sd	t	p
Logical Memory						
Immediate Memory	39	5.05	49.2	6.14	-3.87	.018
Delayed Memory	21.5	4.93	32.5	5.2	-5.00	.015
Learning	3.8	2.17	3.8	2.77	.000	1
Retention	73.9	9.25	91.5	7.85	-5.98	.009
Hopkins Verbal Learning Test						
Immediate Memory	24.4	5.8	22	5.4	1.472	.215
Delayed Memory	8.2	3.4	6.6	3.6	4.0	.016
Learning	3.2	1.92	4.2	.84	-1.41	.230
Retention	82.2	15.02	65.8	31.89	1.98	.120
Recognition	11.4	.89	10.6	1.67	1.63	.178
Rey-Osterrieth Complex Figure Test						
Immediate Memory	16.5	14.14	12.25	13.08	.5667	.111
Delayed Memory	15.5	16.97	14.25	15.91	1.667	.344
Retention	46.15	42.21	47.7	41.72	-4.43	.141
Recognition	18.5	.71	19.0	2.83	-.333	.795
Brief Visuospatial Memory Test						
Immediate Memory	11.67	6.51	16.67	8.96	-1.64	.243
Delayed Memory	5.67	2.52	7.0	4.58	-.610	.604
Learning	3.33	1.53	4.67	2.89	-1.51	.270
Retention	100.0	0.0	86.67	23.09	1.0	.423

Table 12

Paired T-Tests of Individual Measures at t1 and t2 for the Treatment Group

	Pre-surgery raw scores		2 week post-surgery raw scores			
	Mean	Sd	Mean	Sd	t	p
Logical Memory						
Immediate Memory	39.3	6.02	44.7	3.5	-3.67	.067
Delayed Memory	26	5.03	26.67	2.9	-.305	.789
Learning	6.0	2.65	5.33	3.06	.756	.529
Retention	92.7	6.4	82.0	7.8	2.71	.113
Hopkins Verbal Learning Test						
Immediate Memory	24.6	3.13	23.8	2.59	.625	.566
Delayed Memory	10.0	2.45	8.75	2.36	1.67	.194
Learning	4.2	1.64	3.2	2.17	1.2	.298
Retention	99.5	14.64	88.75	14.64	1.35	.270
Recognition	10.8	1.3	10.6	1.14	.343	.749
Rey-Osterrieth Complex Figure Test						
Immediate Memory	19.25	1.77	24	2.12	-1.73	.334
Delayed Memory	18.25	.35	24.25	.35	-12.0	.053
Retention	60.05	5.3	93	26.87	-2.16	.276
Recognition	20.5	2.12	21.0	1.41	-1.0	.50
Brief Visuospatial Memory Test						
Immediate Memory	11.0	8.54	16.67	2.89	-.873	.475
Delayed Memory	3.67	2.31	7.33	2.31	-1.38	.303
Learning	2.67	2.52	3.0	1.0	-.250	.826
Retention	82.0	18.52	103.67	19.76	-2.18	.161

Table 13

Paired T-Tests of Individual Measures at t2 and t3 for the Treatment Group

	2 week post-surgery raw scores		6 week post-surgery raw scores			
	Mean	Sd	Mean	Sd	t	p
Logical Memory						
Immediate Memory	44.7	3.51	45.3	9.5	-.154	.892
Delayed Memory	26.7	5.03	30.33	7.09	-3.05	.093
Learning	5.3	3.1	2.3	.58	1.44	.286
Retention	82	7.8	96.3	4.04	-5.96	.027
Hopkins Verbal Learning Test						
Immediate Memory	23.8	2.59	24.6	5.03	-.384	.721
Delayed Memory	8.75	2.36	8.75	2.36	.775	.495
Learning	3.2	2.17	4.0	1.0	-.825	.456
Retention	88.75	14.64	84.75	27.02	.293	.789
Recognition	10.6	1.14	10.4	1.82	.408	.704
Rey-Osterrieth Complex Figure Test						
Immediate Memory	24.0	2.12	24.25	6.72	-.077	.951
Delayed Memory	24.25	.35	26.75	6.01	-.625	.644
Retention	93.0	26.87	89.0	19.8	.121	.923
Recognition	21.0	1.41	21.5	2.12	-1.0	.50
Brief Visuospatial Memory Test						
Immediate Memory	16.67	2.89	15.0	1.0	.945	.444
Delayed Memory	7.33	2.31	7.33	.58	0.0	1.0
Learning	3.0	1.0	4.0	1.0	-1.0	.423
Retention	103.67	19.76	105.67	9.81	-1.23	.913

Table 14

Paired T-Tests of Individual Measures at t1 and t3 for the Treatment Group

	Pre-surgery raw scores		6 week post-surgery raw scores			
	Mean	Sd	Mean	Sd	t	p
Logical Memory						
Immediate Memory	39.3	6.02	45.3	9.5	-1.52	.203
Delayed Memory	26	5.03	30.33	7.09	-2.06	.108
Learning	6.0	2.65	2.3	.58	1.108	.330
Retention	92.7	6.4	96.3	4.04	-2.69	.055
Hopkins Verbal Learning Test						
Immediate Memory	24.6	3.13	24.6	5.03	0.0	1.0
Delayed Memory	8.8	3.42	8.6	2.41	.106	.92
Learning	4.2	1.64	4.0	1.0	.272	.799
Retention	88.4	27.87	87.8	24.38	.031	.977
Recognition	10.8	1.3	10.4	1.82	.784	.477
Rey-Osterrieth Complex Figure Test						
Immediate Memory	19.25	1.77	24.25	6.72	-.833	.558
Delayed Memory	18.25	.35	26.75	6.01	-1.89	.310
Retention	60.05	5.3	89.0	19.8	-1.63	.350
Recognition	20.5	2.12	21.5	2.12	--	--
Brief Visuospatial Memory Test						
Immediate Memory	11.0	8.54	15.0	1.0	-.846	.486
Delayed Memory	3.67	2.31	7.3	.58	-3.05	.093
Learning	2.67	2.52	4.0	1.0	-.658	.578
Retention	82.0	18.52	105.67	9.81	-2.0	.184

Illustrations of Logical Memory performance revealed variability in the patterns of memory. For example, Figures 6 and 7 shows that the treatment group has very little improvement in immediate and delayed memory from time 1 to time 2 compared to the placebo group. However, from time 2 to time 3, there is a sharper improvement in the treatment group compared to the placebo group. Figure 8 illustrates that learning decreases for the treatment group at each time point; however, the placebo group improves from time 2 to time 3. On the other hand, Figure 9 shows that retention increases for the placebo group at each time point; however, retention declines for the treatment group from time 1 to time 2, but improves from time 2 to time 3.

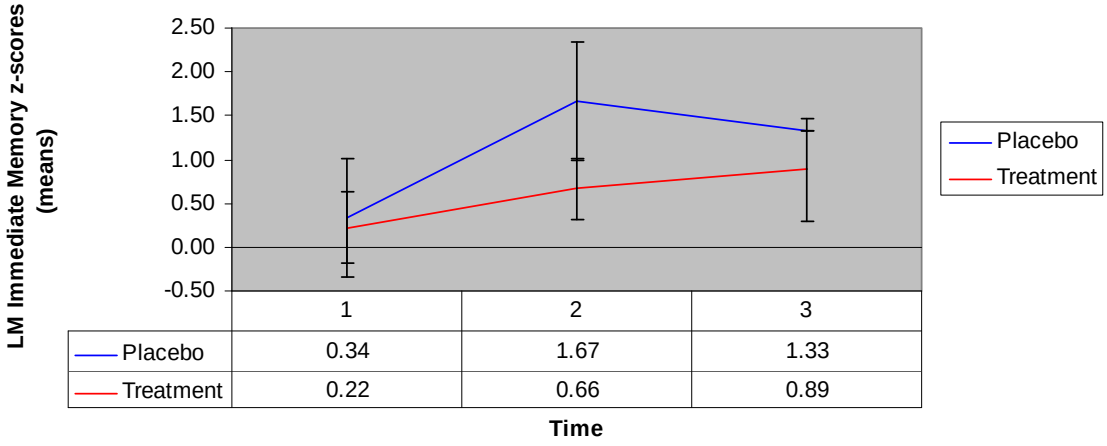


Figure 6. Logical memory (immediate memory) at each time point by group

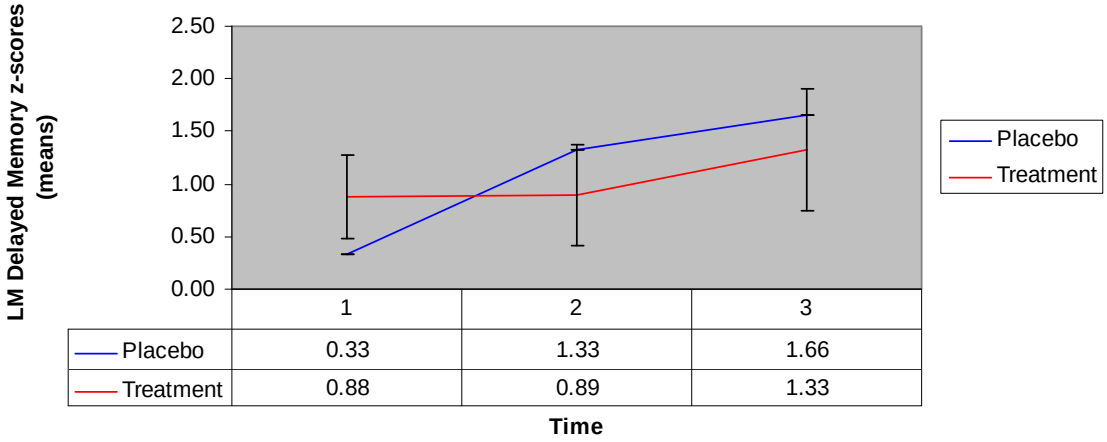


Figure7. Logical memory (delayed memory) at each time point by group

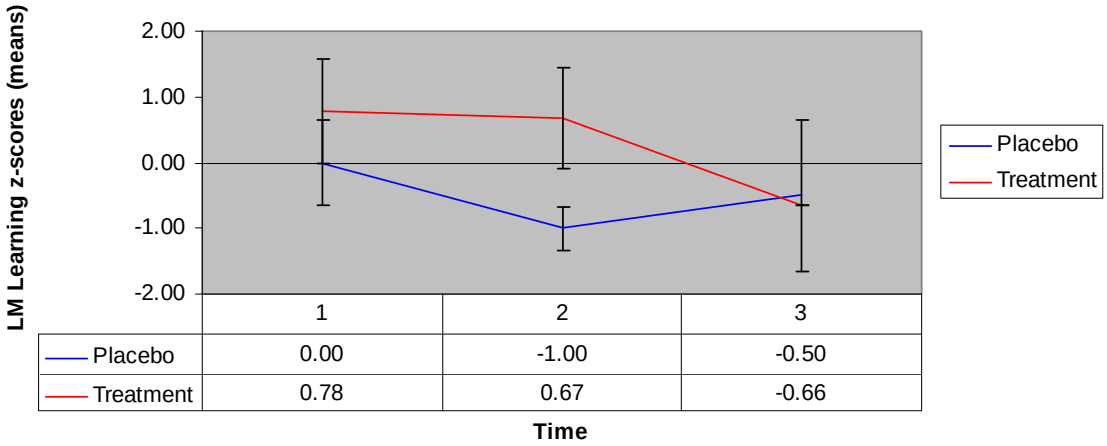


Figure 8. Logical memory (learning) at each time point by group

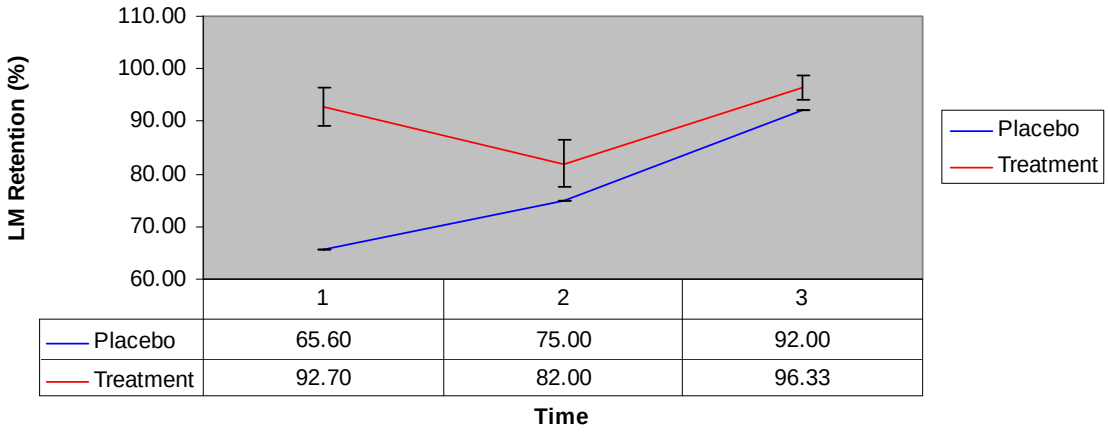


Figure 9. Logical memory (retention) at each time point by group

Hopkins Verbal Learning Test-Revised

For the placebo group, there were no significant differences from time 1 to time 2 or time 2 to time 3 on any of the HVLT-R variables (see Tables 9 and 10). However, a near significant decrease was reached from time 1 to time 3 on delayed memory [t(4) = 4.0, p=.02] (see Table 11). For the treatment group, there were no significant differences from time 1 to time 2, time 2 to time 3, or time 1 to time 3 (see Tables 12-14).

Illustrations of HVLT-R scores revealed variability in the patterns of memory. For example, Figure 10 shows less decline on immediate memory in the treatment group compared to the placebo group from time 1 to time 2; and, from time 2 to time 3, the treatment group improves while the placebo group declines. Figures 11 and 12 illustrate declines in delayed memory and retention for both groups at each time point; however, slightly less declines are observed for the treatment group. Learning patterns illustrated in Figure 13 show that the treatment group declines from time 1 to time 2 while the placebo group remains relatively stable. However, from time 2 to time 3, learning sharply

improves for the placebo group, but remains relatively stable for the treatment group. Figure 14 illustrates that the treatment group improves on recognition from time 1 to time 2, while the placebo group shows declines. However, both groups decline from time 2 to time 3.

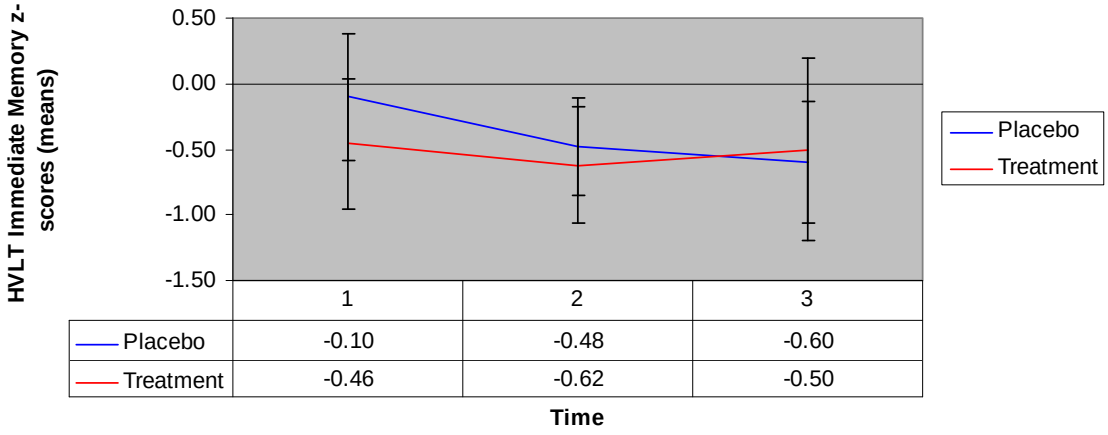


Figure 10. HVLT-R (immediate memory) at each time point by group

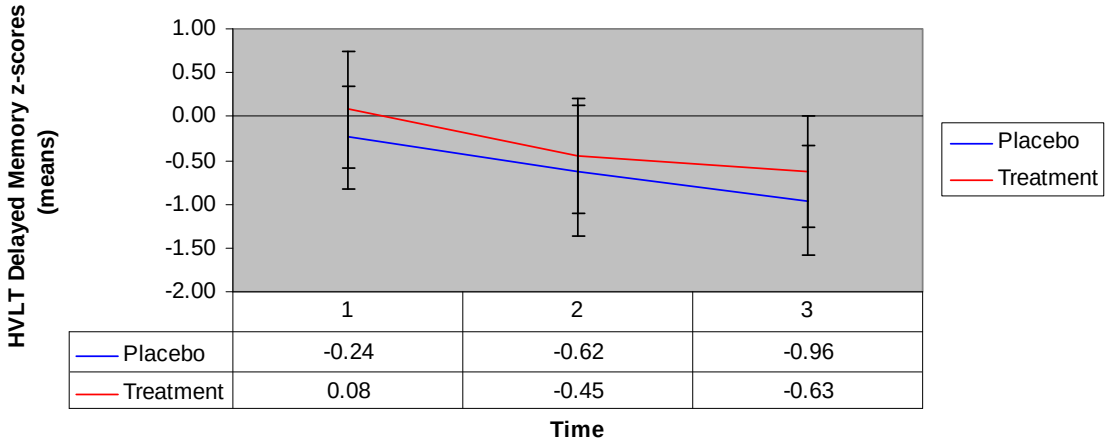


Figure 11. HVLT-R (delayed memory) at each time point by group

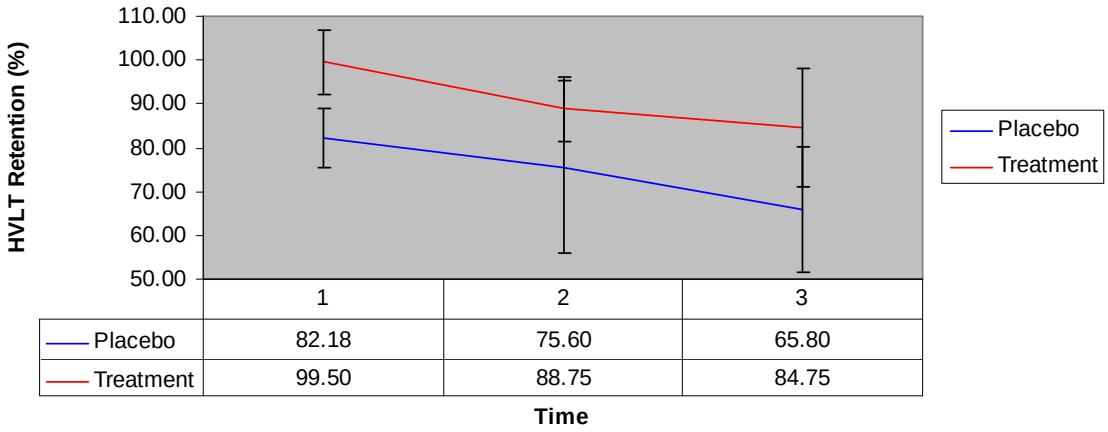


Figure 12. HVLT-R (retention) at each time point by group

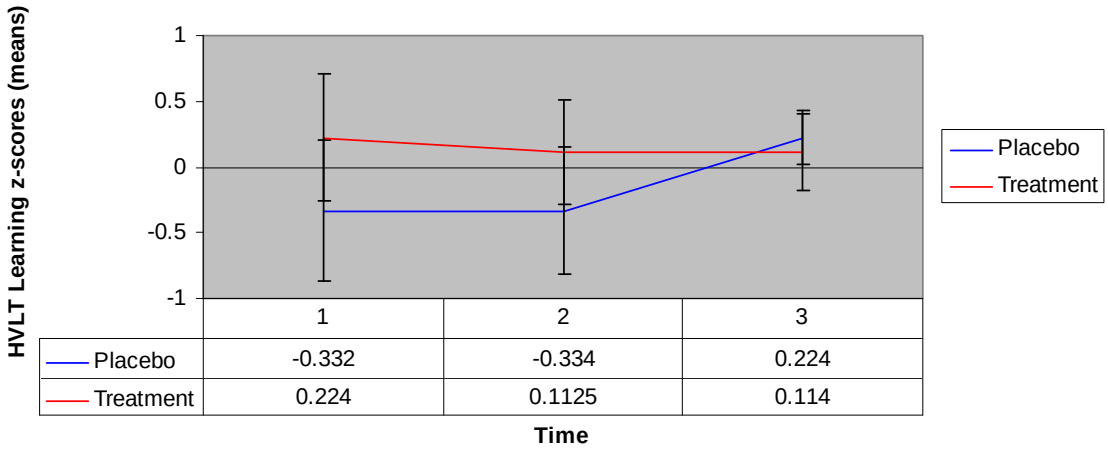


Figure 13. HVLT-R (learning) at each time point by group

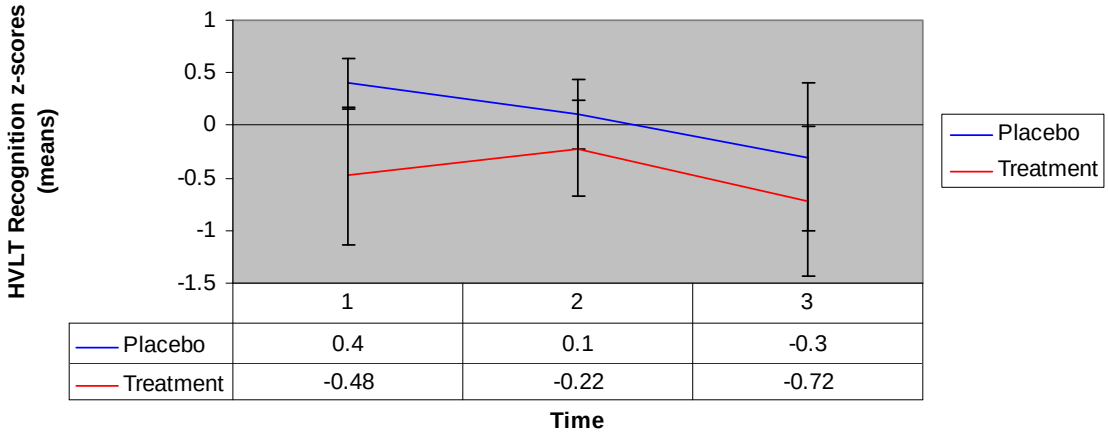


Figure 14. HVLT-R (recognition) at each time point by group

Rey-Osterrieth Complex Figure Test with Recognition

For the placebo group, there were no significant differences from time 1 to time 2, time 2 to time 3, or time 1 to time 3 (see Tables 9-11). For the treatment group, a near significant change was reached from time 1 to time 2 on delayed memory [t(1) = -12.0, p=.05] (see Table 12) with better performances from time 1 to time 2, but no significant differences from time 2 to time 3 or time 1 to time 3 (see Tables 13 and 14).

Illustrations of RCFT scores largely revealed improvements from time 1 to time 2 for the treatment group compared to the placebo group in immediate memory, delayed memory, and retention (see Figures 15-17). Similarly, from time 2 to time 3, the treatment group remained stable or continued to improve for immediate and delayed memory (see Figures 15 and 16). However, the treatment and placebo groups showed slight declines from time 2 to time 3 on retention (see Figure 17). Figure 18 illustrates improvements in the treatment and placebo groups for recognition from time 1 to time 2;

however, the treatment group continued to improve from time 2 to time 3, while the placebo group declined.

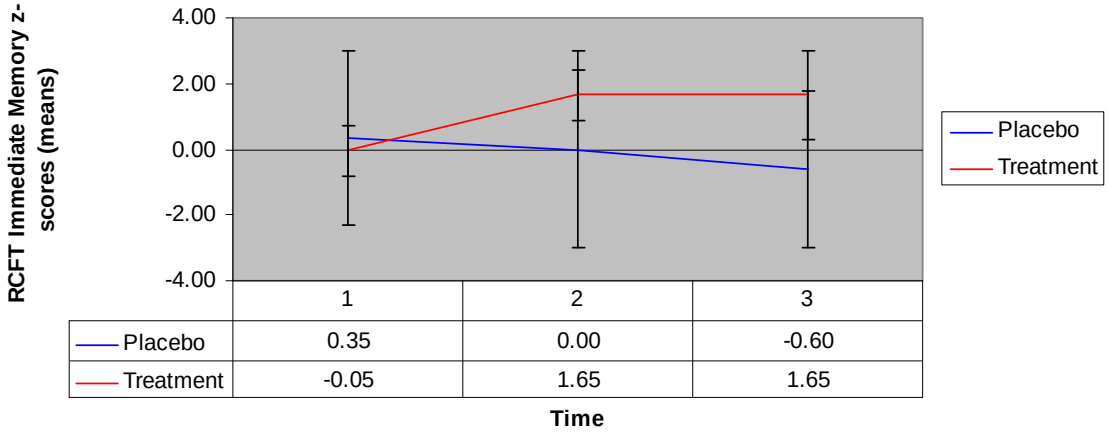


Figure 15. RCFT (immediate memory) at each time point by group

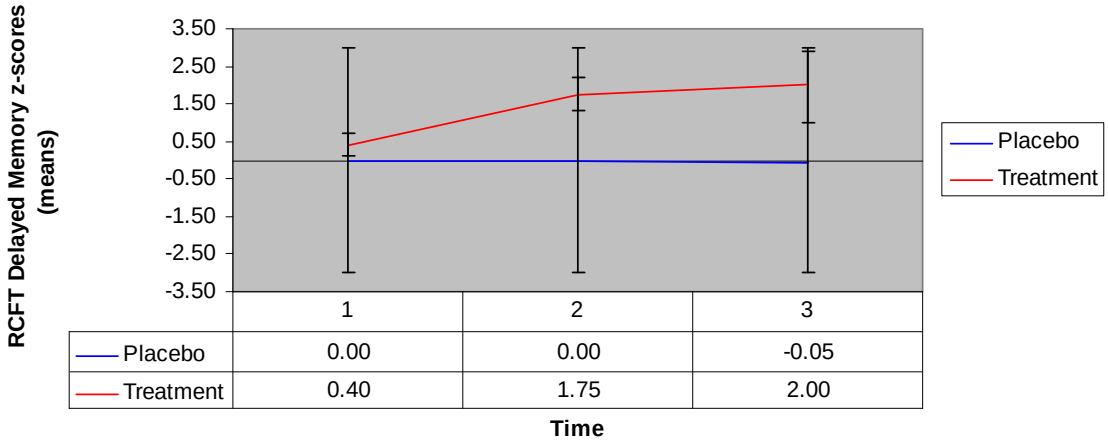


Figure 16. RCFT (delayed memory) at each time point by group

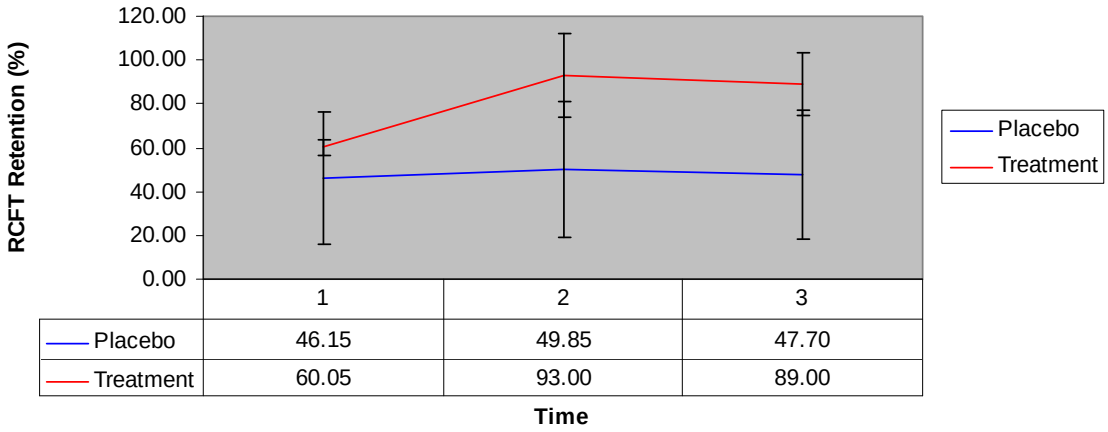


Figure 17. RCFT (retention) at each time point by group

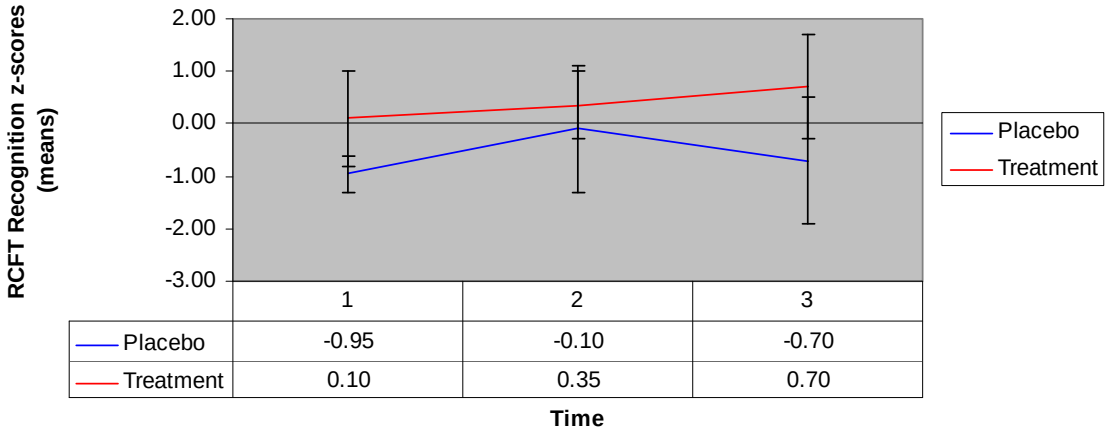


Figure 18. RCFT (recognition) at each time point by group

Brief Visuospatial Memory Test-Revised

For both the placebo and treatment groups, there were no significant differences from time 1 to time 2, time 2 to time 3 or time 1 to time 3 (see Tables 9-14). Illustrations of BVMT performance revealed variability in the patterns of memory. For example, Figure 19 shows improvements in immediate memory from time 1 to time 2 for treatment

and placebo groups; however, from time 2 to time 3, the treatment group shows greater decline from time 2 to time 3. Figure 20 reveals greater improvements in delayed memory for the treatment group compared to the placebo group from time 1 to time 2; however, from time 2 to time 3, the treatment group remained relatively stable while the placebo group improved slightly. Although the placebo group showed greater improvements on learning from time 1 to time 2, the treatment group continued to improve from time 2 to time 3 while the placebo group declined (Figure 21). Figure 22 illustrates improvements in retention at each time point for the treatment group. However, the placebo group declined from time 1 to time 2 and then improved slightly at time 3.

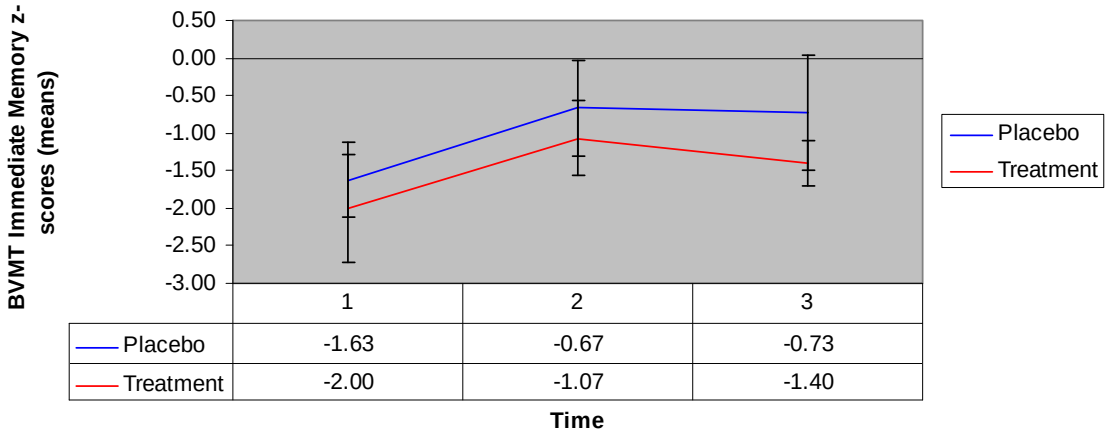


Figure 19. BVMT (immediate memory) at each time point by group

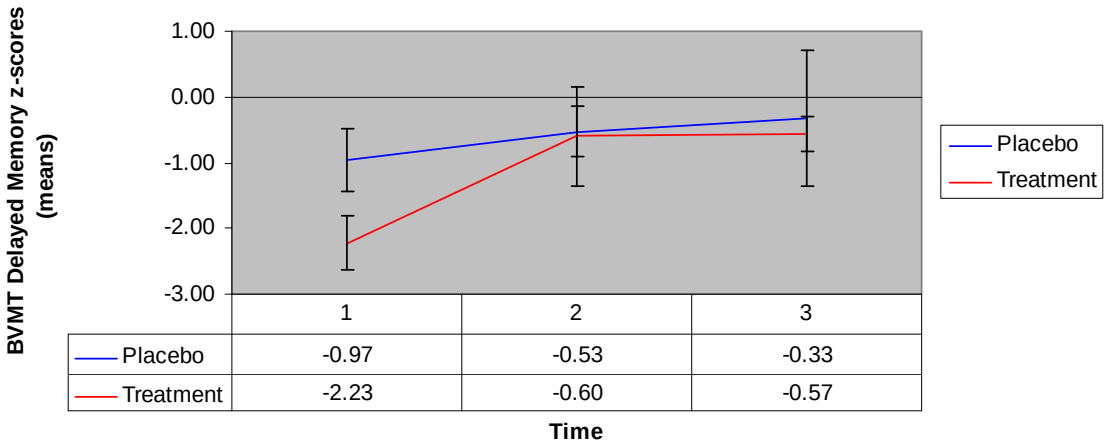


Figure 20. BVMT (delayed memory) at each time point by group

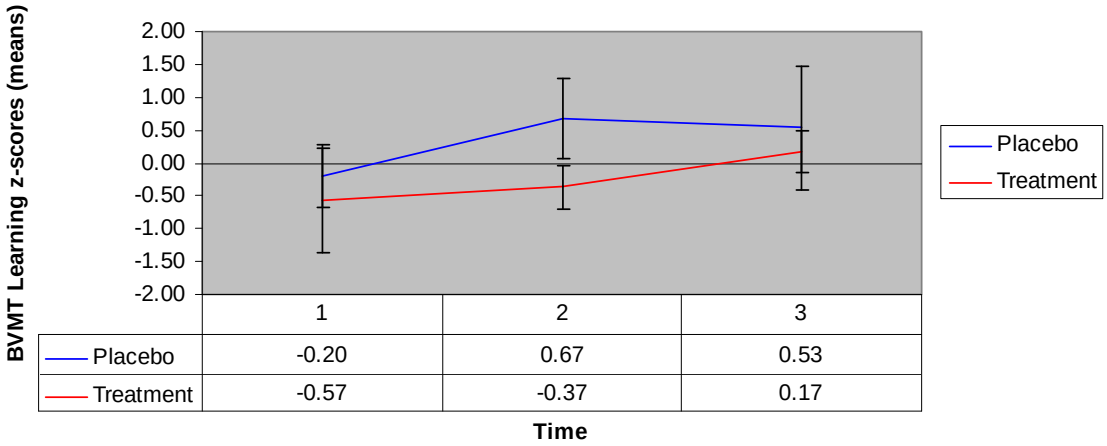


Figure 21. BVMT (learning) at each time point by group

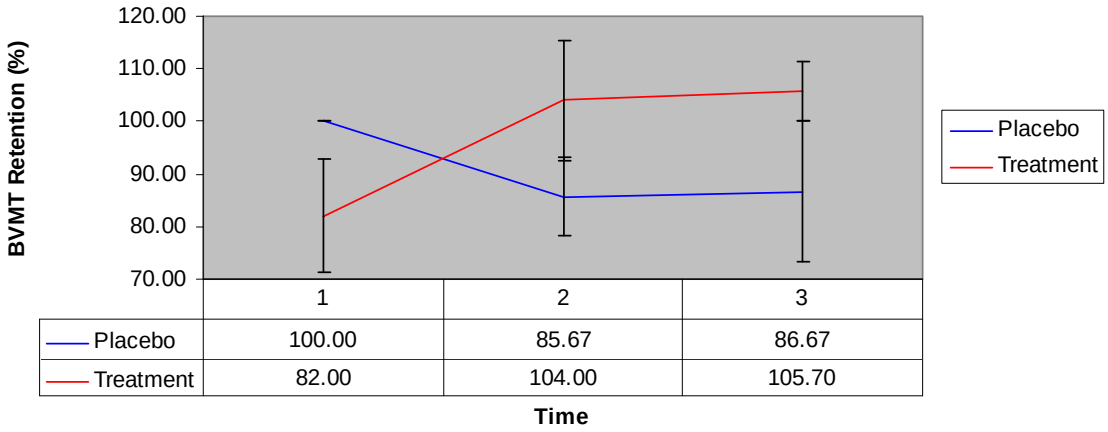


Figure 22. BVMT (retention) at each time point by group

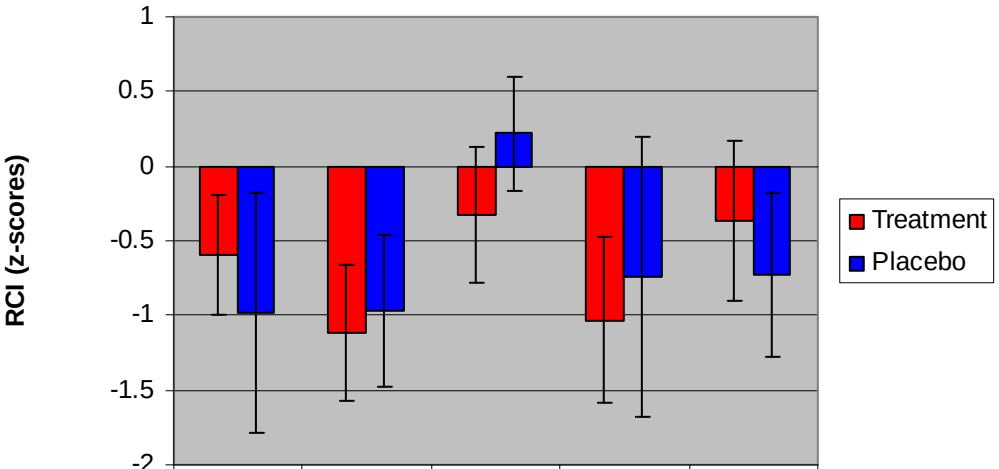
Incidence of Impairment or Improvement

In order to quantify the incidence of clinical impairment/improvement on memory functions, the mean z-score change score was calculated for the treatment and placebo groups for each composite score for the components of memory (time 1 to time 2, time 2 to time 3 and time 1 to time 3). Impairment or improvement was operationally defined as a decline or improvement of 1 standard deviation in the individual's z-score change. This method of defining impairment has been utilized in previous research (Kneebone et. al, 1998).

Reliable Change Indices

Reliable change indices (Chelune, et al. 1993) were calculated for most of the memory measures (e.g., RCFT immediate memory & delayed memory; HVLT-R immediate memory, delayed memory, learning, retention & recognition; and BVMT immediate memory & delayed memory) in order to determine if a statistically significant

and reliable change in memory performance exists after accounting for expected practice effects. The patterns of performances that showed one group performing worse or better than the other on the components of memory for HVLT-R, RCFT, and BVMT remained relatively the same from time 1 to time 2 demonstrating that practice effects do not account for the changes observed (see Figures 23-25). Independent samples t-tests on reliable change indices demonstrated no significant differences between the treatment and placebo groups on any of the HVLT-R or BVMT variables; however, the two groups differed on RCFT delayed memory performances with better scores for the treatment group (p=.07).



	Immediate Memory	Delayed Memory	Learning	Retention	Recognition
Treatment	-0.598	-1.12	-0.326	-1.03	-0.366
Placebo	-0.978	-0.968	0.218	-0.736	-0.73

Figure 23. Reliable change indices (RCI) for HVLT-R memory measures by group (time 1 to time 2)

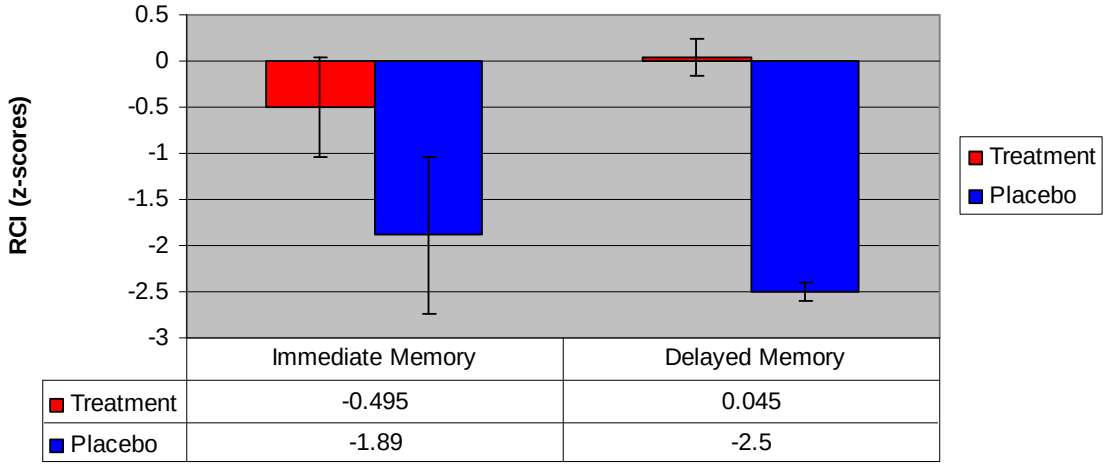


Figure 24. Reliable change indices (RCI) for RCFT memory measures by group (time 1 to time 2)

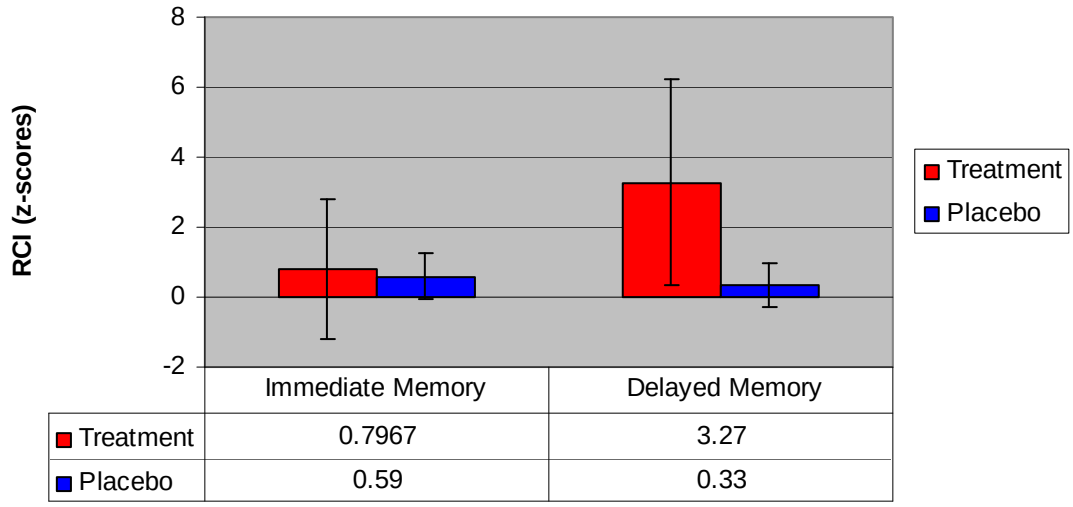


Figure 25. Reliable change indices (RCI) for BVMT memory measures by group (time 1 to time 2)

Table 15 illustrates the instances of clinical impairment/improvement over all time periods for each memory composite within all the tests. It identifies the number of individuals impaired or improved (by time point, group, memory composites, and individual tests). Specifically, it shows a significantly greater number of instances of

clinical declines for the placebo group and fewer for the treatment group from time 1 to time 2 across all memory composites ($X^2 = 4.5$; p=.03). More specifically, there were individuals who had impairments across all tests (usually more than one test). However, from time 2 to time 3 and time 1 to time 3, they are almost similar in the number of instances of clinical declines and improvements ($X^2 = .733$; p=.39; $X^2 = .06$, p=.82 respectively). Although the instances of impairments are higher in the placebo group than the treatment group from time 1 to time 2, it is important to note that the treatment group had 2 individuals with clinical impairments compared to the placebo group that had 3 individuals. From time 2 to time 3, both treatment and placebo groups had 3 individuals with clinical impairments in each group.

Table 15

Incidences of Memory Performance Declines and Improvements

	t1-t2 Treatment		t1-t2 Placebo		t2-t3 Treatment		t2-t3 Placebo		t1-t3 Treatment		t1-t3 Placebo	
	Dec.	Imp.	Dec.	Imp.	Dec.	Imp.	Dec.	Imp.	Dec.	Imp.	Dec.	Imp.
Composite												
Immediate									1			
Delayed	1								1			
Learning		2	1	1		1	3	1	1	1	2	1
Retention				1	1	1			2			2
Recognition	1	1		2		2	1	1		1		1
Individual Measures												
LM imm.			2 (1,2)				1 (2)				2 (1,4)	
LM del.			1 (2)						1 (9)		4 (2,3,4, 5)	
LM learn						1 (7)		1 (1)		1 (7)		1 (1)
LM reten.					1 (8)				2 (7,9)		3 (2,4,5)	
RCFT imm.			1 (2)		1 (7)				1 (7)			
RCFT del.			2 (1,2)		1 (7)				1 (7)			
RCFT recog.												
BVMT imm.	1 (10)	1 (9)			1 (9)					2 (8,10)		1 (3)
BVMT del.		1 (9)				1 (9)		1 (3)				1 (3)
BVMT learn							1 (4)	1 (3)	1 (9)	1 (8)	1 (4)	
BVMT reten.					1 (8)		1 (4)		2 (8,10)			1 (3)
HVLT imm.			1 (1)			1 (8)						1 (1)
HVLT del.	1 (9)		2 (1,3)						1 (6)	2 (9,10)		
HVLT learn												
HVLT reten.	1 (9)		1 (3)		1 (8)	1 (10)		2 (2,4)	2 (6,8)	2 (9,10)		2 (2,3)
HVLT recog.	1 (10)		2 (1,3)			2 (6,8)	1 (1)	1 (2)		1 (10)		1 (2)
TOTAL	**4**	**2**	**12**	**0**	**7**	**6**	**4**	**6**	**11**	**9**	**10**	**8**
Trt. Decline	22											
Trt. Improve	17											
Pla. Decline	26											
Pla. Improve	14											

*Numbers outside the parentheses are the number of individuals that have impairments or improvements. Numbers within the parentheses are the actual subject numbers given to the patients at the time of testing.

Outliers

Outliers were examined for HVLT-R, BVMT-R and Logical Memory. RCFT outliers were not examined given that the two groups only had 2 individuals in each

group and the elimination of outliers would not give an accurate picture of the pattern of performances. There were no outliers given the criteria mentioned above for Logical Memory. For BVMT-R, one outlier was removed for delayed memory. Figure 26 illustrates the pattern of performances. Notably, the pattern does not change from the illustration with the outlier. For HVLT-R, several outliers were removed for delayed memory, retention and recognition. The treatment group demonstrates a decline on delayed memory from time 1 to time 2; however, the placebo group demonstrates an improvement. On the other hand, from time 2 to time 3, the treatment group remains relatively stable while the placebo group sharply declines. For retention, the placebo group increases from time 1 to time 2; however, the treatment group decreases from time 1 to time 2. However, from time 2 to time 3, both groups decline slightly. For recognition, both groups decline from time 1 to time 2; however, from time 2 to time 3, the placebo group improves while the treatment group remains stable (Figures 27-29).

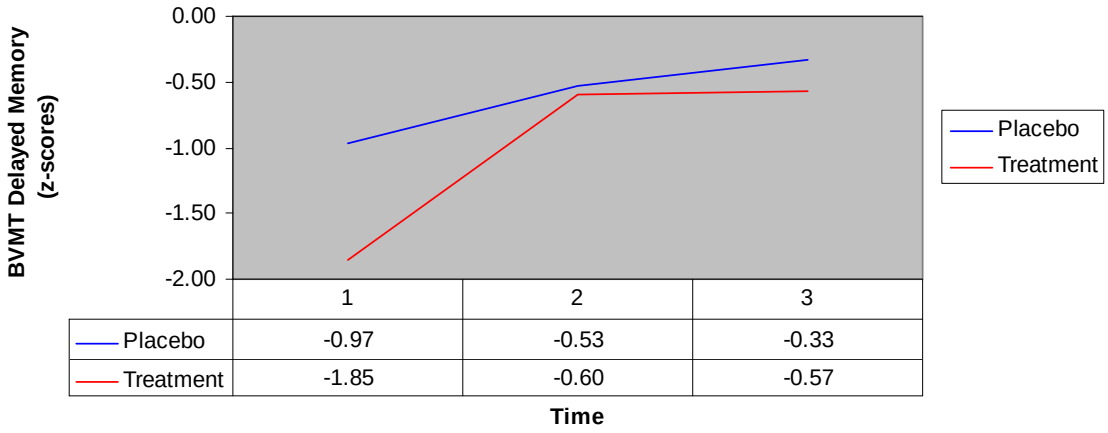


Figure 26. BVMT-R delayed memory (without outliers)

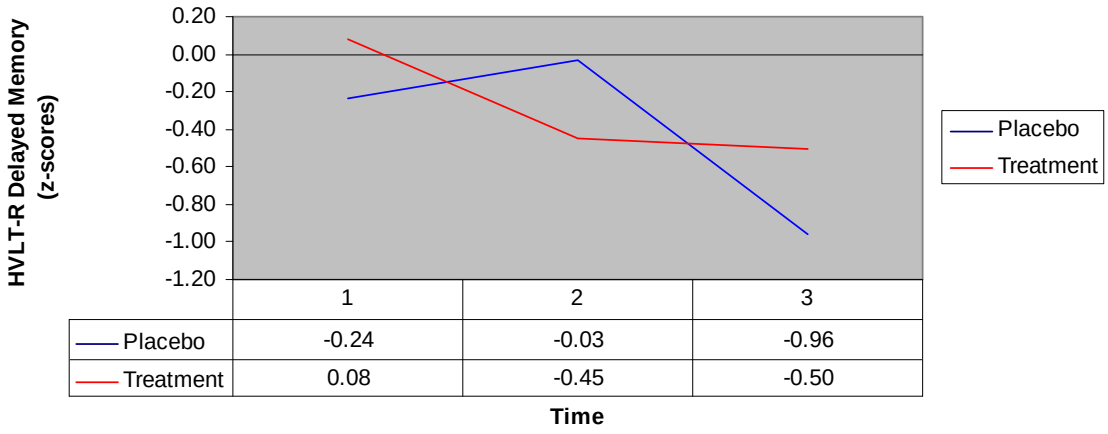


Figure 27. HVLT-R delayed memory (without outliers)

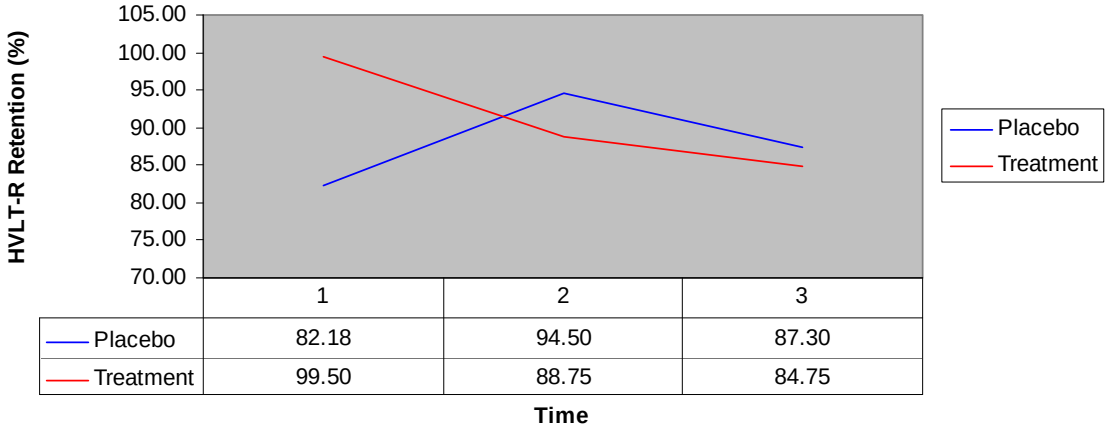


Figure 28. HVLT-R retention (without outliers)

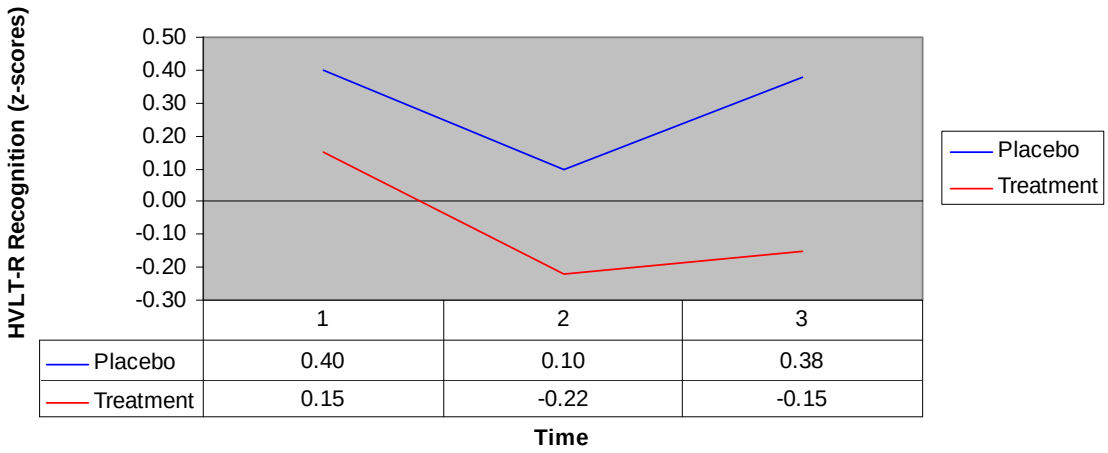


Figure 29. HVLT-R recognition (without outliers)

Effect Sizes

Given that each of the individuals differed in their baseline scores, it was important to take this into account and calculate the effect size of the change scores between the groups from time 1 to time 2 period (as the two groups differed most from each other during these time periods). Results revealed a very large effect size (1.61-3.19) between the groups for each of the memory domains (i.e., immediate memory, delayed memory, retention and recognition), with the treatment group performing better at time 2. Although the learning effect size showed a very large effect between the groups, the placebo group was performing better at time 2 than the treatment group.

CHAPTER FOUR

DISCUSSION

Although many studies have demonstrated significant declines in cognitive functioning after cardiac surgery, limited studies have focused on possible preventative and treatment options for reducing postoperative cognitive dysfunction. Pomegranate has shown promise as a neuroprotective agent against cognitive impairment in animal models, but has not been explored in human models of brain disease or injury. Given this, the focus of this study was to examine whether pomegranate might similarly protect against memory impairment in individuals with heart disease treated with cardiac surgery. Positive findings have broad implications for individual patients, health, and treatments for heart disease.

Demographics

Comparison of demographic data for the treatment and placebo groups revealed that although there were no detectable significant differences between groups on age, education and estimated IQ, the placebo group was older, and had a higher estimated IQ compared to the treatment group. Similarly, no detectable significant differences were found on medical history variables (e.g., hypertension, cholesterol, diabetes, and smoking history); however, it was qualitatively observed that there was a greater number of individuals with hypertension, high cholesterol, diabetes, and history of smoking in the treatment group.

Memory Composites

The results of the study revealed that there were no significant differences between groups in the amount of change in any composite memory component from before to after surgery. The implication of such results is that pomegranate did not have a significant effect on memory performance in this sample. No significant memory changes were found in any composite memory component for any time period, with the exception of the treatment group who performed better on delayed memory at time 3 when compared to their baseline score. Although research has demonstrated significant early cognitive declines after cardiac surgery with some improvement after the early period, this study did not support those findings for this sample. Negative findings may reflect design limitations such as low power due to too few subjects.

Visual analyses of the data are intriguing and may suggest developing trends in the data not otherwise identified by statistical significance. In particular, memory performance tended to decline very little for both groups, although the literature predicted otherwise. Instead, it tended to remain stable and, for some, improved from before to after cardiac surgery. This can be explained by the fact that most of these individuals may have a moderate to high cognitive reserve (which was not calculated), based on their IQ and education. Research has shown high cognitive reserve to be a protective factor in cognition (Corral, Rodriguez, Amenedo, Sanchez & Diaz, 2006) and even protective in heart disease and cardiac surgery (Ropacki, Bert, Ropacki, Rogers & Stern, 2007). Perhaps if there were more subjects with greater variability in cognitive reserve, we may have observed a different picture, one that is consistent with the literature. Improvements

may be attributed to the better blood flow in the heart and subsequently, the brain after surgery.

Observable trends for the treatment group to improve on memory from before surgery (baseline) to after surgery (most notably from baseline to time 2) is in direct contrast to the lack of improvement for the placebo group. Although the exact mechanisms of the pomegranate workings cannot be determined, early postoperative improvements in memory may indicate that variables associated with the surgery may have been acted on by the pomegranate (e.g., hypoxia and ischemia which are often observed early postoperatively), thereby protecting some components of memory. Similar performances and improvements for both groups from time 2 to time 3 suggest a diminished effect of pomegranate, possibly due to the diminishing impact of hypoxia and ischemia on memory beyond the immediate postoperative period.

Further exploration of the results reveals certain patterns within each memory composite which are important to note as they may provide a context for understanding these emerging differences between groups. More specifically, in the treatment group, a sharp improvement in immediate memory is observed early after surgery; however, there is only a modest improvement from time 2 to time 3 in this group. A similar pattern is observed for delayed memory and retention. However, in the placebo group, relatively little change is observed in immediate memory, while decline on delayed memory and a decline in retention are observed early after surgery. Yet, similar to the treatment group, the placebo group shows improvement from time 2 to time 3. This may further support the claim that the pomegranate is acting upon the early postoperative hypoxia associated with the surgery, as opposed to the disease state.

In order to facilitate the interpretation of the substantive results as opposed to relying on statistical significance, the results may also be examined in the context of effect size. Calculations of effect size revealed negligible or diminishing effects for most of the components of memory (e.g., immediate memory, delayed memory, learning, and recognition). Although a couple of the tests (e.g., HVLT-R and BVMT) have alternate forms, the other tests do not (Logical Memory and RCFT); thus, practice effects may have been differentially impacting results and, moreover, may have skewed the effect sizes and power of the measures to detect true changes in memory functioning. Additionally, it is important to note that at baseline, there are mostly larger effect sizes than at time 2 or time 3 for many of the above mentioned components. This may suggest that the two groups differed in their performances on the components of memory at baseline, but due to the small sample size, the analyses may not have been able to detect statistically significant changes in memory performance. One component of memory (retention), in contrast, demonstrated the opposite pattern over time. It is important to note that the effect sizes for retention started out small at time 1, but significantly increased from time 2 to time 3 suggestive of a relationship between retention and treatment effect. Overall, examination of the effect sizes of all of the components examined in this study reveals that there may be some relationship between retention and the intervention. Since research has implicated the role of the medial temporal lobe and hippocampus in episodic memory (see Review – Budson, 2009), we can deduce that these are the areas that are being affected after surgery for the placebo and treatment groups. Additionally, research on CABG surgery has demonstrated neuronal loss and susceptibility for hypoxia in the temporal lobe and more specifically, the hippocampus.

However, it may be that pomegranate may be providing some protection from the effects of hypoxia leading to better outcomes in retention rates compared to the placebo group.

Illustrations of learning demonstrate that the placebo group performs better from time 1 to time 2 and from time 2 to time 3 compared to the treatment group. This may be explained by certain characteristics of the HVLT-R. The HVLT-R learning score is considered to be a measure of working memory that requires executive skills including organization and strategy (Rudolph et al., 2006). It has been demonstrated that patients with frontal lobe lesions fail to utilize memory strategies to enhance the encoding and retrieving of information (Baldo and Shimamura, 2002), which may in turn impact the ability to freely recall the information. Figure 30 demonstrates that in the current study, the placebo group performs better than the treatment group on an attentional/working memory task (WAIS-III Digit Span). Their better executive skill may be a factor contributing to the observed learning pattern. Research has also demonstrated an association between cardiovascular risk factors and the development of cerebral white matter lesions. These lesions have been associated with executive dysfunction (see review - Kuo and Lipsitz, 2004). Given that the frequency of individuals with hypertension, cholesterol, diabetes and smoking is higher for the treatment group than the placebo group, we can speculate that the treatment group may have greater frontal lobe impairments compared to the placebo group. Additionally, the mechanism for damage in the frontal lobe (related to cardiovascular risk factors), and subsequent learning difficulty, may be different from the mechanism for damage occurring after surgery (e.g. transient ischemia/hypoxia). Given what we understand about the areas most susceptible to hypoxia (e.g. hippocampus), we may be able to speculate that individuals may not benefit

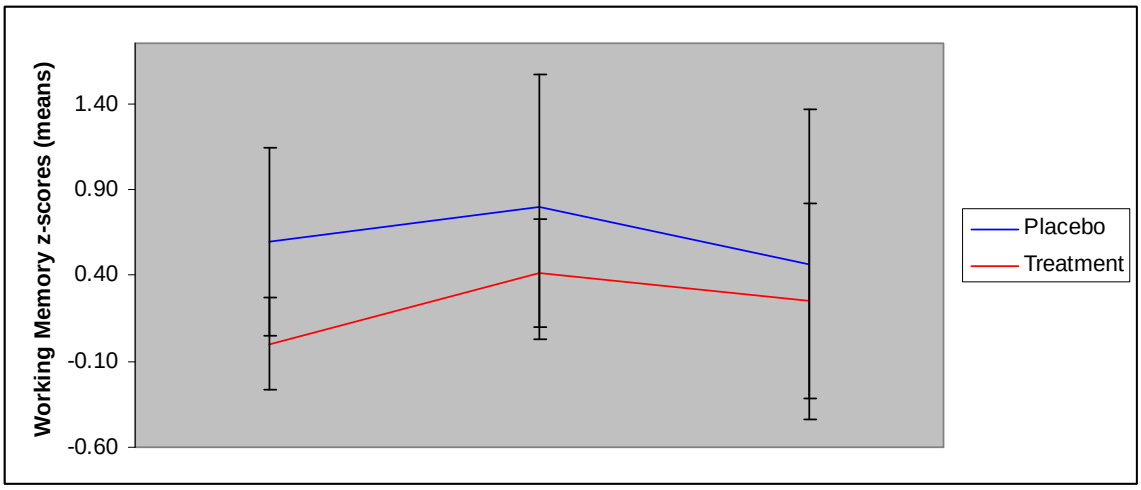


Figure 30. Working memory (WAIS-III Digit Span) by group

from pomegranate supplementation with regards to using strategies to learn (which can be considered a frontal lobe function).

Illustrations of recognition memory performance demonstrate that the treatment group performs better from time 1 to time 2 compared to the placebo group, implicating a role of pomegranate supplementation in this time frame; however, both groups decline sharply from time 2 to time 3. Given this information, it may be possible that there are some lasting effects of the surgery or the disease states that is impacting the temporal regions. Research has shown that cognitive functions began their return to baseline levels after the early postoperative. However, research has also demonstrated that there are some individuals that continue to experience long term cognitive declines. This finding further supports the idea that the pomegranate is benefiting in the early postoperative period, but demonstrating diminishing effects as there are diminishing instances and effects of hypoxia over time.

Individual Memory Measures

In order to further explore the contributions of each neuropsychological test to the composite measures of the components of memory, each test was examined over time. First, it is important to note that baseline memory functioning on each of the individual measures for both the treatment and placebo groups were largely in the average to high average ranges with the exception of a visual learning and memory measure (BVMT). This exception will be discussed later in the context of the format of the tests. Moreover, although both treatment and placebo groups scored within the average to high average range on measures of verbal memory, they performed in the lower to middle range of average on a rote/noncontextual verbal memory test (HVLT-R), which was in contrast to their performances in the mid to high average range on contextual memory tests (Logical Memory, RCFT). Overall, improvements or declines within each of the measures are more likely to represent true change given that they are performing as expected (e.g., within the normal range) and there is no instance of regressing to the mean in such a case; however, improvements on BVMT on successive testing points could be a function of regression to the mean, as this sample was initially impaired at baseline on this measure.

Logical Memory

The placebo group had significant improvements on immediate memory, delayed memory and retention from time 1 to time 3. This pattern of consistent improvement over time may be a function of cardiac surgery restoring blood flow in the heart which in turn affects blood flow to the brain; in such circumstances, it would be expected that at least minimal improvements would continue to be made over the observed six week period. The treatment group had significant improvements on immediate memory from

time 1 to time 2 and on retention from time 2 to time 3 (and time 1 to time 3). However, the early postoperative changes (improvements) in immediate memory suggests the pomegranate's impact may be most powerful early after surgery, when the hippocampus has perhaps taken the biggest "hit" by surgery. Comparing these two groups, graphically, there is variability in the performances. Some of this variability can be contributed to practice effects as some patients were administered this test at time 2, while others were not (although there were no detectable significant differences, the fact that some tests were administered more times than others may create some variability over time). Additionally, since some patients were not administered this test at time 2, there is a smaller sample size at this point (5 patients instead of 10). Therefore, we may not be observing an accurate picture of the treatment effects from time 1 to time 2.

Hopkins Verbal Learning Test-Revised

This test was considered to be important in capturing the effects of pomegranate as this test was administered to all the patients at each time point (unlike the other tests) and had alternate forms. However, graphical illustrations of the results were not as expected with a great deal of variability observed in the patterns of the memory process for both groups. The placebo group had no significant declines or improvements from time 1 to time 2, or time 2 to time 3; however, they did demonstrate significant decline from time 1 to time 3 on delayed memory. The treatment group had no significant declines or improvements from time 1 to time 2, time 2 to time 3 or time 1 to time 3. Since delayed memory scores are a product of initial learning and immediate memory (that is, how much can be recalled after a delay is directly dependent upon how much information is initially learned and immediately encoded), evaluation of learning and

immediate memory scores may inform our understanding of these patterns in delayed memory performance. More specifically, these patterns suggest the observed decline in delayed memory for the placebo group stems from diminished learning and immediate memory from time 1 to time 2, as evidenced by declines in learning scores and declines in immediate memory scores. This interpretation is further supported in light of similar retention scores across the groups – both groups ultimately retained a similar amount of the information initially learned, though that amount was less in the placebo group. As mentioned previously, HVLT-R not only has a strong memory component, but it also has a component that is tapping into the workings of the frontal lobe (e.g. organization of the words into categories for easier encoding, and subsequent recall of the information after a delay). Therefore, the findings may be due to contributory effects of the frontal lobe.

Rey-Osterrieth Complex Figure Test

The placebo group had no significant declines or improvements from time 1 to time 2, time 2 to time 3 or time 1 to time 3 on any of the components of memory. The treatment group had a significant improvement from time 1 to time 2 on delayed memory. Illustrations of RCFT performance demonstrated less variability in the patterns of the components of memory (although some variability still existed) than the above mentioned tests with largely better performances for the treatment group. It is observed that the treatment group has better immediate memory from time 1 to time 2, suggesting that they may be learning the information in a more effective way compared to the placebo group (although there is no way to calculate a learning score for RCFT). It is important to note that the task already provides a context and organization for the patients (unlike HVLT-R where the individuals are required to organize information in order to

encode more effectively), so the frontal lobes may not be involved the same way as they are with HVLT-R. Therefore, if the patients are able to encode the information more effectively due to the inclusion of a context, this will not be one of the factors contributing to the delayed memory and retention performances. Therefore, the improvements observed at the level of immediate memory, delayed memory and retention may be a function of the pomegranate acting upon the hypoxic states early postoperatively. For the placebo group, we observe a relatively flat (slightly declined) immediate memory which may be translating into relatively flat scores for both delayed memory and retention. It is important to note that visuospatial functioning could also impact their ability to encode and remember the information. Therefore, poor visuospatial functioning could be contributing to the lower scores for the placebo group. However, it is important to note that both groups only had two individuals in each group due to the discontinuation of the test later on in the study.

Brief Visuospatial Memory Test-Revised

Placebo and treatment groups had no significant declines or improvements from baseline to time 2, time 2 to time 3 or time 1 to time 3 on any of the components of memory. Illustrations of BVMT performance, however, also noted variability in the patterns of the components of memory. For both immediate and delayed memory, an increase is observed for both groups from time 1 to time 2. However, as mentioned previously, both groups are performing significantly below average at time 1; therefore, the better performances may be a function of regression to the mean. However, it is important to note that the treatment group has a sharper increase for delayed memory compared to the placebo group. When observing their learning scores, we see that the

treatment group has a relatively flat learning from time 1 to time 2 (unlike HVLT-R where we are seeing declines in learning which may be affecting their memory). So it can be suggested that when learning is stable from time 1 to time 2 (they are encoding as much information at time 2 as they are during time 1), the increases in delayed memory, and subsequently retention, can be a function of the pomegranate workings in the early postoperative period. Furthermore, we see that although the placebo group has better performances in learning and immediate memory from time 1 to time 2, they are unable to retain the learned information to the level that the treatment group is retaining.

Comment on Test Characteristics

We observe that while the treatment group has lower performances on BVMT, they have higher performances on the RCFT compared to the placebo group. This is an unexpected finding given that both of these tests are assessing visual memory and we would expect the pattern of each group's performances to be the same within each task. However, this task is different from the previous described visual memory measure (RCFT) in several ways. First, the RCFT is a task that has a contextual component to it (which can assist in learning as it is already organized and doesn't require the individuals to put in effort in doing so), while the BVMT does not. The RCFT has one complex figure, while the BVMT has multiple simple figures. Moreover, the BVMT has a time and learning component (each patient is administered multiple trials of the same figures), while the RCFT does not (the stimulus is presented on only one trial). It is important to note that although the trials of learning is to facilitate the encoding process, if the patients are having difficulties with attention and become overwhelmed by the amount of

information presented in 10 seconds, learning will not be facilitated despite the multiple trials. Furthermore, comparing HVLT-R and BVMT (which are both assessing learning and memory), treatment group performances demonstrate declining learning for HVLT and a slight increase on BVMT suggesting that the organizational component of HVLT may be impacting learning and subsequently memory. However, the lack of decline on BVMT suggests that there may be an effect of the pomegranate on learning when the task is not heavily relying on the frontal lobe.

Comment on Individual Measures

Given all the variability, it appears that the declines and improvements on the individual measures may be canceling each other out when composites are created, thereby washing out statistically detectable differences in the composites. However, it is important to note that retention was one component of memory that was consistently better for the treatment group than the placebo group on almost all of the tests (except HVLT-R). Retention is a score that takes into account both the individual's immediate memory and delayed memory. This is the most informative measure of an individual's memory, as it represents how much an individual remembers relative to how much was initially learned. Therefore, even if an individual's learning and immediate memory is poor, retention reflects more directly how much information is remembered. The differences observed in retention may best reflect differences between groups and possibly may be the most informative variable to provide support for the impact of pomegranate on memory.

Overall, examination of the various memory tests suggest that the patients in the treatment group are performing better from time 1 to time 2 on non-verbal measures (indicative of involvement of the right hemisphere) compared to the verbal measures (indicative of involvement of the left hemisphere). Therefore, it is suggestive that pomegranate is more beneficial for dealing with the hypoxic effects of the right hemisphere than the left hemisphere. This could be explained by animal studies that have examined the effects of hypoxia on the left and right hemisphere. Studies have shown that the neurochemical activity in the right hemisphere is more susceptible to the effects of hypoxia (Nalivaeva et al., 1995; Nalivaeva, Klementev, Plesneva, Chekulaeva & Zhuravin, 1998).

Comment on Outliers

In order to determine whether the patterns of performances were being driven by outliers, a thorough examination of the data points was conducted. Data points that were +/- 3 standard deviations were considered to be outliers. Given that the RCFT only had two individuals in each group, outliers were not removed from this test. Logical Memory had no outliers. One individual data point was removed from BVMT delayed memory and several outliers were removed from HVLT-R delayed memory, retention and recognition. Although the pattern of BVMT delayed memory did not change once the outlier was removed, HVLT-R patterns changed once the outliers were removed. Although the treatment group's pattern of performance does not change much from Figure 11 (Delayed Memory), the placebo group improves from time 1 to time 2. This follows the patterns observed on other tests which support that this group may have a

high cognitive reserve which could be protective of cognitive declines. The continued decline of the treatment group from time 1 to time 2 may be due to a more severe disease state (therefore, more compromised cognitive functions) compared to the placebo group as they present with a higher frequency of individuals with vascular risk factors. However, the relative stability of performances from time 2 to time 3 for the treatment group and declines for the placebo group may be a function of the pomegranate workings. With regards to retention, the placebo group increases from time 1 to time 2; however, the treatment group decreases from time 1 to time 2. As mentioned above, this could be due to the differences in the severity of disease states and cognitive reserve. In contrast, from time 2 to time 3, the treatment and placebo groups decrease slightly. Recognition patterns show the treatment group and placebo group declining from time 1 to time 2. However, the placebo group shows greater improvements from time 2 to time 3 while the treatment group increases slightly.

Incidence of Impairments/Improvements

Patients' performances were examined individually in order to determine the incidence of memory impairments and/or improvements. First, their composite performances were compared to their previous performances (e.g. time 1 to time 2, time 2 to time 3, and time 1 to time 3) by creating a change z-score. Using the one standard deviation method, it was determined that there was no significant difference between the groups in the number of instances of clinical memory impairments or improvements at each time point. This may be a function of the limitations of this study which will be addressed later (e.g. sample size). Second, since a couple of these tests did not have

alternate forms, measures were examined individually while controlling for practice effects using reliable change indices. The highest incidence of clinical memory impairments (1.65 standard deviations below the mean) was observed in the placebo group from time 1 to time 2 (e.g., more patients were impaired on several tests of memory). However, from time 2 to time 3 and time 1 to time 3, the placebo and treatment groups did not differ significantly from each other (e.g. similar instances of memory impairments). This again demonstrates the protective effects of pomegranate early after surgery. Although there was a higher incidence of memory impairments across the tests, it is important to note that there were two individuals in the treatment group and three individuals in the placebo group with impairments from time 1 to time 2. Notably, the two impaired individuals in the treatment group performed poorly on tasks that required them to learn and encode the information, which are considered frontal lobe functions. Although all memory tests require learning and encoding of information, there are certain tests (e.g., Logical Memory and RCFT) that are contextual by design and do not require the individual to create context or organization in order to efficiently learn the information. Despite being potentially more impaired, we do not observe the declines expected on executively-demanding tasks in those with such risk factors and frontal dysfunction. The relative lack of decline may reflect some protection from pomegranate.

Limitations

There were a few limitations to this study that should be considered. First, the sample size was very small especially since the goal of this study examined the difference between two groups. This limited the power of the study and led to an inability to detect

statistical significance. The chosen tests at the initial start of the study may not have been the most useful in determining the effects of pomegranate on memory as they did not have alternate forms; therefore, leading to possible effects of practice. This in turn may have compromised the reliability of the composites. Due to the limited sample size, we were unable to examine the effects of covariates (e.g. demographics, medical variables, surgical variables) on the results. Additionally, given the research on frontal dysfunction of patients with vascular risk factors, it would have been useful to control for frontal lobe functions in order to determine whether frontal dysfunction may be affecting temporal lobe functioning. Additionally, it would have helped to have certain surgical variables, such as cerebral oxygen desaturation (Slater et al., 2009), that examine hypoxia or ischemia in order to support the idea that pomegranate is indeed protecting the hippocampus from hypoxia. Another limitation was that we were unable to track their diet (e.g. fruits/vegetable servings each day in order to ascertain the amount of antioxidants they intake), compliance with the pills, and exercise or activity level of these patients. Moreover, an analysis of their urine could have helped to confirm the amount of antioxidants they were taking in.

Future Research and Treatment

Although there are several limitations to this pilot study, it provides direction for future research and treatment. Results of this study suggest that there is some effect of pomegranate in the early postoperative period after cardiac surgery. Given all the variables and components of memory measured in this study, it appears that examination of retention rates will yield the most informative results for future studies. It has been

noted that “there is only one memory system but there are multiple processes operating on this system or multiple ways of accessing its contents” (Squire, 2004). Given what we now know about the possible factors affecting memory functioning, a similar study should be conducted on a much larger scale and over a longer period of time, incorporating various perioperative variables (e.g. hypoxia, ischemia), individual differences (e.g. cognitive reserve) and other cognitive functions (e.g. frontal lobe functions). Furthermore, future studies should compare the effects of pomegranate on the memory functioning of patients with CAD or valvular disease (without cardiac surgery) and those with cardiac surgery in order to further understand the mechanisms of pomegranates within these disease states. It would also be helpful to correlate the results of cognitive tests with brain imaging before and after cardiac surgery in order to locate where the most damage is present before and after surgery and where any improvement is occurring in the brain after pomegranate supplementation.

Implications

Although the treatment and placebo groups are performing similarly at time 3, the critical time period of interpatient variability seems to be from time 1 to time 2. The most important implication for patients is that if we are able to offset the amount of memory decline immediately after surgery, then their long term prognosis may be better-according to a previously mentioned study by Newman et al. (2001). Alternatively, there are important implications for both patients and healthcare personnel. Research has shown that there are several factors that predict prolonged intensive care and length of hospital stay, including intraoperative cerebral oxygen desaturation (Slater et al., 2009).

If pomegranate is indeed targeting hypoxic mechanisms, then it may lead to shorter intensive care unit and hospital stays, thereby decreasing hospital costs and costs to the healthcare system. Another general implication for individuals is to increase engagement in health behaviors that are easily incorporated into daily life, are relatively free of negative side effects, and are comparatively inexpensive, in order to limit the number of factors (e.g., hypertension, high cholesterol and smoking) which put them at greater risk for heart disease necessitating cardiac surgery and the subsequent cognitive decline that commonly occurs after cardiac surgery. Ultimately, continued research conducted in a similar vein would lead to better treatments that improve the outcome of cardiac surgery and the cognitive well-being of the multitude of men and women who undergo these types of surgeries.

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