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THROMBOLYSIS AND EARLY SPEECH AND LANGUAGE RECOVERY AFTER STROKE

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THROMBOLYSIS AND EARLY SPEECH AND LANGUAGE RECOVERY AFTER STROKE

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements

for the degree of Doctor of Philosophy

in the College of Health Sciences

at the University of Kentucky

By

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ABSTRACT OF DISSERTATION

THROMBOLYSIS AND EARLY SPEECH AND LANGUAGE

RECOVERY AFTER STROKE

Speech and language impairments after left hemisphere stroke are life altering. Neuroprotective interventions, such as tissue plasminogen activator, or tPA, are utilized to diminish the impact of the stroke on functional ability.

The purpose of this study was to examine speech and language recovery in the first three months after stroke in individuals with aphasia and to further investigate any differences between individuals who did and individuals who did not receive tPA, using objective speech and language measures.

Twenty-six individuals, thirteen of whom received tPA and thirteen who did not, suffering from first-ever left hemisphere stroke with resulting aphasia were enrolled and completed repeated speech and language assessments within 24 hours after stroke, at one and two weeks after stroke. A three month assessment also included an additional quality of life measure.

Findings indicate that both individuals who did and those who did not receive tPA demonstrated significant gains in language skills. Results also suggest that the individuals who received tPA have better outcomes at three months compared to those who did not. This is clinically significant as it helps provide prognostic information about the use of tPA and informs decision making for speech pathologists within the acute care hospital.

KEYWORDS: Stroke, Aphasia, Language, Thrombolysis, tPA

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THROMBOLYSIS AND EARLY SPEECH AND LANGUAGE RECOVERY AFTER STROKE

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Chapter One- Introduction

Overview

Stroke is a leading cause of disability and death throughout the world. While the incidence of new strokes has remained stable, death rates have decreased over the last 10-15 years (Benjamin et al, 2017). As a result, more individuals are living out their lives coping with and being treated for residual effects of a stroke. Considering the financial impact on the healthcare economy, the American Stroke Association (ASA; Benjamin et al, 2017) estimated the total direct cost of care for stroke in the United States in 2013 was $17.9 billion, with a mean expense per patient of $5,232. The ASA (Benjamin et al, 2017) also projected that America would spend $1.5 trillion in stroke care between the years 2005-2050, with many of these dollars spent on rehabilitation of individuals recovering from stroke. As such, it is important to focus attention on the efficacy of current clinical practices intended to minimize the disabling consequences of stroke.

An estimated 800,000 individuals experience a cerebrovascular accident each year, with 610,000 of these being first-time strokes (Benjamin et al, 2017). Ischemic strokes, often created by clots that either form at the location of the stroke or travel from elsewhere in the body, account for 87% of all strokes. The remaining 13% are hemorrhagic, occurring when a blood vessel ruptures and bleeds into the brain (Benjamin et al, 2017). Because ischemic strokes damage the brain differently than hemorrhages, these two types of strokes have different prognoses and clinical treatment pathways.

Aphasia, an acquired language disorder affecting input and output modalities resulting from damage to the brain's language dominant hemisphere, is a frequent

consequence of ischemic stroke (Brookshire, 2007). Aphasia is often accompanied by neuromotor speech disorders such as apraxia of speech and unilateral upper motor neuron dysarthria (Wambaugh & Shuster, 2008) that further compromise a person's communicative ability. Aphasia is present in 15-30% of individuals with stroke at time of admission to the acute care hospital (Engleter et al, 2006; Inatomi, et al, 2008; Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001; Lazar et al, 2010; Maas et al 2012) and its consequences are frequently long term. Studies using objective language tests reveal that the majority of people with aphasia never completely recover their pre-morbid communicative abilities (Klebic, Salihovic, Softic, & Solihovic, 2001; Laska et al, 2001). In addition to the impact on an individual's receptive and expressive language skills, aphasia has profound functional, psychosocial, and emotional consequences for patients and families. These include activity limitations such as inability to participate in conversations, make phone calls, respond to emails, read the paper and carry out other tasks considered normal in one's culture (Elman, 1994; Kagan & Gailey, 1993; Kagan, 1998), participation restrictions reflected in abandonment of formerly enjoyed activities, fewer social contacts (Cruice, Worrall, & Hickson, 2006; Dalesman et al., 2008), and strained interpersonal relationships (Croteau, LeDorze, & Morin, 2008; Doyle, McNeill, Hula, & Mikolic, 2003; Michallet, Tretreault, & LeDorze, 2003; Simmons-Mackie, Kearns, & Potechin, 2005). Researchers have also reported people with aphasia and their families have a reduced quality of life and can suffer from depression, loss of confidence, and reduced self-esteem (Shadden, Hagstron, & Koski, 2008; Simmons-Mackie, King, & Beukelman, 2013).

Scientists have continually sought to develop treatments that would minimize and/or prevent neurological damage resulting from a stroke thereby reducing the disabling consequences of conditions such as aphasia. Pharmacological and procedural interventions have been implemented clinically by physicians as an early treatment for ischemic strokes. The aim of these treatments is to improve clinical outcomes and reduce functional impairment by restoring vascularization to the brain, potentially preventing tissue damage. One such neuro-protective intervention is administration of intravenous tissue plasminogen activator (tPA), using the mechanism of *thrombolysis,* or breaking up clots. tPA is intended to dissolve the blood clot to help restore blood flow through the vessel and hopefully, limit damage to brain tissue. Since its approval for use by the U. S. Food and Drug Administration (FDA) in 1996, tPA has been receiving more widespread clinical use (Fang, Cutler, & Rosen, 2010).

tPA is administered only under specific conditions. Due to the risk of hemorrhage with tPA, it is used solely with ischemic type strokes. Moreover, the benefits of tPA are known to be maximized if it is administered during a small window of time. Initially, the time window set for administration of tPA by the FDA was three hours after stroke symptom onset. More recently, clinical trials suggest this window can be expanded to 4.5 hours for certain eligible patients (Cheng & Kim, 2015; NINDS, 1995; Hacke et al, 1995; Hacke et al, 1998; Hacke et al, 2008; Clark et al, 1999; Clark, Albers, Madden, & Hamilton, 2000). While national rates of tPA are slowly increasing, administration remains low (Benjamin et al, 2017). In part, this is due to the short time frame for administering tPA, not seeking medical attention for symptoms of a stroke until after the time frame has elapsed (Eissa, Krass, Levi, Sturm, Ibrahim, & Bajorek, 2013; Maze &

Bakas, 2004), geography, and seeking early treatment at smaller hospitals where tPA is not available (Adeoye, Hornung, Khatri, & Kleindorfer, 2011; Benjamin et al, 2017). In hospital systems with dedicated stroke units and stroke programs, however, administration rates of tPA reportedly range from 15-38% (Cheng & Kim, 2015; Lichtman et al, 2009). Interestingly, utilization has continued to be low, even after the expansion of the time window to 4.5 hours.

Research on the effects of tPA on clinical outcomes for survivors of ischemic stroke is ongoing and will be reviewed in Chapter 2. Currently, it is not clear if tPA significantly impacts clinical outcomes for individuals with ischemic stroke, regardless of whether or not these individuals manifest aphasia. There are multiple challenges faced by researchers seeking to conduct prospective studies on the effects of tPA on outcomes for ischemic stroke survivors. With the cascade of events that accompany a new stroke, it is difficult to objectively assess patients shortly after onset of stroke and arrival at the emergency room. Barriers within the acute care hospital such as patient access, urgency of medical intervention, reduced length of stay associated with a trend to discharge patients as soon as possible, and spontaneous recovery of deficits have precluded rigorous study in this area.

The goal of this study was to examine and compare expressive speech and language changes for patients with first-time ischemic stroke with aphasia who did and did not receive tPA. Aphasia was selected as a target symptom to study the effects of tPA for three reasons. First, patients who demonstrate overt signs of aphasia in the ER after ischemic stroke are likely to receive tPA (Dickey et al, 2010; Di Legge, Fang, Saposnik, & Hachinski, 2005; Engelter et al, 2006; Kohrmann et al, 2008; Maas et al,

2012). Secondly, aphasia frequently accompanies a left hemisphere ischemic stroke and is a source of long-term disablement for many patients. Any treatment that potentially reduces the severity of conditions such as aphasia warrants careful study, particularly a treatment that costs $6,000-7,000 to provide (Mozzaffarian et al, 2016). Finally, the primary investigator is a Speech-Language Pathologist, Director of the Chandler Medical Center Speech-Language Pathology Services, and member of the Stroke Care Team and has a vested interest in improving and developing contemporary assessment and treatment procedures for patients with aphasia from stroke in the acute care hospital.

Primary Research Questions

Question 1: Do persons with aphasia following a first-ever left hemisphere ischemic stroke improve speech and language skills in the first two weeks post onset?

Hypothesis: Individuals with speech and language deficits after first-ever left hemisphere stroke will perform significantly better on speech and language tasks over multiple time points during the first two weeks after stroke. The null hypothesis is that the participants will make no significant improvement over two weeks on verbal output measures, specifically repetition of digits, polysyllabic words, confrontational picture naming, and picture description.

Question 2: Do persons with aphasia following a first-ever left hemisphere ischemic stroke who do and do not receive tPA exhibit differences in speech and language recovery in the first two weeks post onset?

Hypothesis: Individuals who receive tPA will perform significantly better on objective speech and language measures in the first two weeks post-onset than those who do not receive tPA. The null hypothesis is that there will be no difference between individuals who do and do not receive tPA on verbal output measures, specifically repetition of digits, polysyllabic words, confrontational picture naming, and picture description.

Question 3: Do persons with aphasia resulting from a first-ever ischemic stroke who do and do not receive tPA differ on speech, language, and quality of life measures at three months after stroke after receiving speech and language therapy?

Hypothesis: Individuals who receive tPA will perform significantly better on each objective measure at three months compared to those who do not receive tPA. In addition, individuals who receive tPA will have significantly better quality of life, as indicated by a higher score on the Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39), compared to those who did not receive tPA. The null hypothesis is that there will be no difference between individuals who do and do not receive tPA on verbal output measures, specifically repetition of digits, polysyllabic words, confrontational picture naming, and picture description or the SAQOL-39 at 3 months post stroke.

Secondary Research Question

Question 4: In persons with first-ever left hemisphere stroke resulting in speech and language deficits, what other relationships are present between demographic, medical, and therapeutic variables and early speech and language recovery?

Hypothesis: The following variables will be significant predictors of early speech and language recovery following first-ever left hemisphere stroke: age, education, gender, location of stroke, comorbidity index, current medications, stroke severity, and amount of speech language therapy received. The null hypothesis is that no variables tested will significantly predict speech and language recovery.

This study is important and unique in several ways. To the knowledge of the investigator, it is the first prospective study to examine speech and language changes in individuals who do and do not receive tPA in a systematic fashion. To date, benefits of tPA on speech and language outcomes have been assumed or examined retrospectively in individual subjects or studies with small sample sizes (Ness, 2012; Cho 2015; Mazza 2012; Sontenini 2009; Mehrpour 2014). Secondly, most studies examining speech and language outcomes for individuals receiving tPA have employed subjective scales and clinical ratings rather than using objective speech and language measures based on patient performance (Denier 2015; Kremer 2013; Maas 2012). Additionally, this study exercises a degree of methodological rigor not used in prior studies by examining speech and language recovery in patients who do and do not receive tPA meeting similar selection criteria. Finally, this study is clinically significant as it provides new information on how thrombolysis may impact the early spontaneous recovery phase after

a stroke. Increased knowledge in this area will help define the role of the speech language pathologist (SLP) early after the onset of a stroke and could potentially help guide the SLP in providing prognostic information for an individual with speech and language deficits.

Chapter Two- Literature Review

Overview

This chapter provides a review of current literature regarding stroke and tPA, supporting the need for this investigation. Following a brief discussion about the impact of stroke, details about tissue plasminogen activator (tPA), its use, and its benefit will be shared. Next, information about aphasia after stroke and prognostic factors for aphasia will be presented. Finally, current literature on the impact of tPA on aphasia will be presented.

Stroke

According to the American Heart Association, someone in the world has a stroke approximately every 40 seconds (Benjamin et al, 2017). Some of these individuals will die but for many of those that survive, long-term disability may be their new reality. Medical and rehabilitative care can be costly and extensive, with individuals experiencing varied long-term deficits. Per person, the average cost, including both direct and indirect costs, of ischemic stroke care is estimated at around $140,000 over the course of a lifetime. This includes thousands of dollars in ongoing rehabilitative care and an average acute care hospital stay of 6 days, compared to 9.5 days in 1990 (Benjamin et al, 2017). Therefore, it is imperative to investigate the impact of various treatments on the rehabilitation of functional outcomes.

Thrombolysis Use

Since its FDA approval in 1996, tissue plasminogen activator (tPA) has been the treatment of choice for individuals with ischemic stroke to achieve thrombolysis. tPA is a protein, generally found on endothelial cells within blood vessels, that helps breakdown blood clots. It is a catalyst to convert plasminogen to plasmin, the enzyme that breaks down the clot (Klabunde, R., 2007). First produced by Genentech in 1982, the drug is manufactured by a recombinant DNA technique, so is often referred to as recombinant tPA (r-tPA). However, for the purposes of this paper, I will consistently use the abbreviation tPA. The drug can be administered either intravenously (IV) or intra-arterially (IA).

Early studies with tPA investigated dosing and safety of the drug, as well as the feasibility of completing early neurological assessments for tPA administration. Dosing of intravenous thrombolysis is generally determined based upon the weight of the person with stroke, calculated as milligrams per kilogram. A two-part series in 1992 examined both dosing and timing of administration. In part one, Brott and colleagues (1992) studied patients who received tPA within a 90-minute timeframe, receiving a range of doses from 0.35-1.08 mg/kg. In part two of the same study, tPA was provided between 91-180 minutes after stroke onset, with one of three doses: 0.6 mg/kg, 0.85 mg/kg, and 0.95 mg/kg (Haley et al, 1992). While some methodological concerns are present in these studies, both found that the incidence of cerebral hemorrhage is significantly correlated to increasing dosage rates, with a maximum threshold of 0.85 mg/kg to limit the risk of hemorrhage. Both of these studies found 40-50% of individuals with a major neurological improvement by 24 hours, measured by use of the National Institute of Health Stroke

Scale (NIHSS). Delzoppo and colleagues (1992) also investigated a group of individuals with varying dosage rates of tPA, measured in million international units with a range of 0.12-0.75 MIU/kg, and found no significant correlation between dosing and risk of hemorrhage. This may be attributed, however, to the lower dosage used in this study. Currently in standard practice, dosage is 0.9 mg/kg.

Guidelines for Administration. Only certain individuals qualify to receive this drug upon admission to the hospital for a possible stroke. Reasons why an individual may not receive the treatment include time restrictions, medical contraindications, patient-specific factors, and physician-specific factors.

The biggest factor in tPA administration is time post onset. FDA approval currently recommends administration of IV tPA if a patient presents to the hospital within a three hour window of stroke symptom onset. Several early large-scale studies on tPA outcomes, known as NINDS (NINDS, 1995), ECASS I (Hacke et al, 1995), ECASS II (Hacke et al, 1998), ECASS III (Hacke et al, 2008), ATLANTIS A (Clark et al, 2000), and ATLANTIS B (Clark et al, 1999), provided initial information to develop current guidelines, including time of administration. Across these studies, authors investigated various windows of administration time between 3-6 hours, differing dosages of tPA, using outcome measures including the NIHSS, Barthel Index (BI), Modified Rankin Scale (mRS), and the Glasgow Outcome Scale, with contrasting results depending on time windows used (NINDS, 1995; Hacke et al, 1995; Hacke et al, 1998; Hacke et al, 2008; Clark et al, 2000; Clark et al, 1999). A pooled analysis of these studies was

subsequently completed and support a favorable functional and survival outcome when tPA is given within 3-4.5 hours (Lees et al, 2010) of stroke onset. Although the FDA has not extended the recommended time for tPA, the American Heart Association has issued a set of guidelines and recommendations for administering tPA within 4.5 hours with specific exclusion criteria, including age greater than 80, use of oral anticoagulants, and an NIHSS of greater than 25 (Cheng & Kim, 2015). The European counterpart to the FDA has also extended its recommended window to 4.5 hours (Cheng & Kim 2015). Therefore, current general practice is administration within a 4.5 hour timeframe of stroke symptom onset.

Although the window of possible administration has been extended to 4.5 hours, in practice, patients have better outcomes, including mortality and function, when they receive tPA more quickly (Prabhakaran, Ruff, & Berstein, 2015), supporting the idea that earlier reperfusion reduces the risk of death and leads to improved functional status. Ahmed and colleagues (2013) compared individuals receiving tPA within 3 hours, between 3-4.5 hours, and between 4.5-6 hours and found that functional independence was highest when the tPA was administered before 3 hours, while mortality was the same across all groups. Similarly, Saver et al (2013) found earlier treatment with tPA to be associated with better outcomes, including improved ambulation, greater chance of discharge to home, reduced mortality, and reduced risk of adverse events such as intracranial hemorrhage. Delzoppo and colleagues (1992) also found that time to treatment was a significant predictor of outcomes and risk of hemorrhage. So while an individual may receive the treatment up to 4.5 hours after stroke onset, it is highly recommended to seek treatment as soon as possible.

Since the time window for administration is small, the decision not to seek care for the symptoms of a stroke immediately by some patients may limit their ability to receive this potentially lifesaving treatment. Individuals are less likely to get this intervention if they are older, arrive later at the hospital, or go to a smaller or non-academic medical center (Fang et al, 2010; Hills & Johnston, 2006). In the area where the current study was completed, many individuals are excluded from receiving tPA because they did not seek medical attention quickly enough, an established issue in many areas (Eissa et al, 2013; Maze & Bakas, 2004).

There are also medical contraindications that may preclude tPA administration. Only individuals with an ischemic stroke, confirmed by CT scan, qualify to receive the drug, due to the risk of additional bleeding, worsening of neurological damage, and death with a hemorrhagic stroke. Even with ischemic stroke, the risk of hemorrhagic conversion of the stroke is of concern. Other medical factors initially thought to be contraindications include recent surgery or current use of blood thinning medications. However, more recently, these are of less concern for some physicians (Fraser, 2018) with more providing the intervention even in the presence of these established risk factors.

Some also argue that tPA should not be given to individuals with a severe stroke. For example, guidelines from the AHA/ASA suggest administering the drug with caution to individuals with an NIHSS of 25 or higher. Supporting this, Davis et al (2008) point out that those with a large stroke will still have significant impairments, even after treatment with tPA, and the risk of hemorrhagic conversion and other complications seem to outweigh the benefits of the drug with this population. Similarly, in the ATLANTIS B

(Clark et al, 1999) trial, in those with NIHSS of greater than 20 and treated with tPA, there was a 100% mortality rate, highlighting the risk of administration in individuals who have a large stroke.

Given the multitude of factors to consider in administration of tPA, neurologists are the bedside decision makers on whether the patient would benefit and should receive the treatment. Therefore, patient outcomes may be impacted by physician-specific factors, specifically physician bias. When a geographically limited group of neurologists were surveyed, they reported that the decision to use tPA was impacted by their own perception of quality of life after a stroke, as well as concern for the cost of implementation (Hovsepian & Karceski 2013; Shamy & Jaigobin, 2013). Additionally, uncertainty in interpreting neuroimaging results is a reported concern among physicians, impacting the decision to administer tPA (Shamy & Jaigobin, 2013).

Age also appears to be a factor that impacts administration and guidelines suggest caution in patients over 80 years. In fact, in the AHA/ASA guidelines, this age threshold is a recommended exclusion criterion when providing tPA between 3-4.5 hours after stroke onset. However, in the International Stroke Trial-3 (IST-3 Collaborative Group, 2012), authors found a significant benefit and limited risks to patients over this age threshold, concluding that age alone should not be a substantial factor in considering use of the treatment.

Considering the multiple reasons that tPA is limited in administration, it is not surprising that its rate of usage is low. Although rates of administration of tPA have increased over the last 20 years, the drug is still underutilized. Fang, Cutler, and Rosen

(2010) reported usage rates less than 1% in 2001. In the first decade of this century, administration rates have reportedly varied between 2-8% for all persons admitted with stroke (Benjamin et al, 2017; Adeoye et al, 2011; Choi, Kang, Kang, Ko, & Bae, 2007; Fang et al, 2010; Hills & Johnston, 2006; Hoffmeister et al, 2013). Notably however, based on the 2015 "Get with the Guidelines" Stroke Quality reports from hospitals with established stroke centers, of the patients arriving at the hospital within two hours from symptom onset, 88% received tPA (Benjamin et al, 2017).

Financial impact. In addition to potentially improved function, tPA appears to have financial benefits that impact the overall healthcare system. Patients receiving thrombolysis have shorter stays in the rehabilitation hospital and are more likely to discharge home, relieving some burden on long-term healthcare facilities (Meyer et al, 2012). In general, the cost of rehabilitation is significantly lowered after a person receives tPA, with estimates that post-acute care rehabilitation costs are reduced by more than six million dollars per 1000 cases of tPA (Fagan, 2010).

Risks of Use. Unfortunately, even though tPA is intended to improve functional outcomes, sometimes the opposite may occur. Cerebral hemorrhaging, with a subsequent decline in neurological functioning or even death, is a potential risk. Therefore, within the context of a patient's clinical presentation, the risk of adverse events with tPA must be strongly considered in relation to the benefit of its use. Many research studies have

investigated specific adverse events with the use of tPA, including mortality rates and development of hemorrhage after intervention, and found varied results.

The majority of the large studies (NINDS, 1995; Hacke et al, 1995; Hacke et al, 1998; Hacke et al, 2008; Clark et al, 1999) previously mentioned found significantly more cerebral hemorrhages post tPA. A 2014 Cochrane review of 27 trials (Wardlaw, Murray, Berge, & del Zoppo), corroborates these results, concluding that patients receiving thrombolytic treatment had an increased risk of hemorrhage. This review also suggests evidence that patients have an increased risk of death and dependence when a hemorrhage occurs. Other studies support an increased risk of death after tPA. Clark and colleagues (2000), found significantly more deaths in those who received tPA. Similarly, the International Stroke Trial-3 (IST-3 Collaborative Group, 2012), a large randomized control trial administering tPA up to 6 hours post onset, found significantly more deaths in the treatment group within the first 7 days.

Other studies do not consistently report increased risk of death after tPA, however. Many of the large randomized controlled trials (NINDS, 1995; Hacke et al, 1995; Hacke et al, 1998; Hacke et al, 2008; Clark et al, 1999) found no significant difference in mortality between groups at three months. De Olivier & Damasceno (2011) reported that administration of tPA was not a significant factor in predicting survival with a population of individuals with stroke. Given the differing results in prior studies, the variability of risk of adverse events warrants the careful consideration by neurologists prior to administration of intravenous thrombolysis.

Functional Outcomes after Thrombolysis

A wealth of literature supports general functional benefits for individuals who get tPA. All of the aforementioned large-scale studies assessed functional change, often defined as "favorable outcomes", based on global scales of function. In 1995, the NINDS study by the National Institute of Neurological Disorders and Stroke, using the NIHSS and mRS, revealed no significant difference between the tPA and non-tPA groups at 24 hours. However, at three months, the tPA group was 30 percent more likely to have minimal or no disability, regardless of location of stroke lesion. In this study, almost half of the tPA group demonstrated a complete or near-complete recovery.

In the first ECASS study (Hacke et al, 1995), authors reported no significant difference in groups at three months when assessing with the BI or mRS. However, in the two follow-up ECASS studies, the results were very different. The second ECASS trial (Hacke et al, 1998) used the mRS as the primary outcome measure on 800 patients in a dichotomized fashion and found a significantly higher level of independence in the tPA group at three months. The final ECASS (Hacke et al, 2008) trial used the mRS and also created a global outcome score, which incorporated the mRS, BI, NIHSS, and the Glasgow Outcome Score. On both measures, with a study group of over 800 subjects, individuals who received tPA demonstrated significantly better outcomes at three months.

In the first ATLANTIS trial (Clark et al, 2000), the primary outcome measure was a decrease of four or more points on the NIHSS, as well as use of the BI and mRS, to assess functional improvement. Interestingly, a significantly higher percentage of

individuals with tPA showed functional improvement at 24 hours but at day 30, the placebo group had better outcomes. On the follow up study, no significant difference in groups was observed at three months, when measuring functional outcomes as "excellent recovery", defined as an NIHSS of 0 or 1. There were also no differences between groups at 30 or 90 days using the BI, mRS, and Glasgow Outcome Scale.

Lees and colleagues (2010) reported findings from a study in which they pooled data from several large-scale studies in an attempt to compensate for various findings across studies. They found a more positive outcome as the onset time decreased and overall more benefits of the treatment when received within the 4.5 hour timeframe. When pooling the mRS scores, there was no difference between treated and untreated individuals when treatment was provided between 4.5-6 hours. However, within the 4.5 hour timeframe the individuals who received tPA demonstrated better outcomes than those who did not. In the International Stroke Trial-3, the window of time was expanded to 6 hours and the outcomes included assessing for individuals who were "alive and independent" with a modified version of the mRS, the Oxford Handicap Score (OHS). Although there was no difference between those individuals who received tPA and those who did not at six months, the OHS scores were analyzed ordinally and there was a favorable shift for the group receiving tPA. Further analysis in this trial did indicate better outcomes if the tPA was administered within three hours, supporting early reperfusion. This supports previously discussed results by various other researchers (Ahmed et al, 2013; Prabhakaran et al, 2015; Saver et al, 2013).

In addition to the large-scale studies, other case and retrospective studies investigated the functional outcomes after tPA. In a single study report on a 98-year-old

individual with a left middle cerebral artery infarct of moderate severity, tPA resulted in complete resolution of symptoms per the NIHSS and complete recanalization of the M1 branch of the artery within 2 hours (Neeb, 2013). A retrospective study of 65 individuals with vertebrobasilar artery occlusion revealed those thrombolized had significantly more favorable functional results, based on subjectively created categories of severity (Hacke, Zeumer, Ferbert, Bruckmann, & del Zoppo, 1988). Another retrospective analysis of individuals with mild stroke, defined as an NIHSS of 6 or less, revealed that 87.2% of the population who received tPA were independent at three months (Nesi, Lucente, Nencini, Fancellu, & Inzitari, 2013). However, in this study an equal proportion of those with favorable and those with unfavorable outcomes received tPA, supporting other variables in recovery.

Several small prospectively completed studies also provide information about recovery of function after tPA, using NIHSS and mRS as outcome measures, both in the early recovery and long term timeframe, generally up to three months post onset. In a study in which very early dramatic recovery was defined as a drop of 10 points in the NIHSS by the end of the tPA infusion, Felberg et al (2002) found that 22% of the individuals with middle cerebral artery (MCA) infarcts receiving tPA had a dramatic recovery and a significantly higher percentage of this group achieved recanalization after infusion. Additionally, these people had significantly better mRS scores at long-term follow up. Two other studies found similar results. Kohrmann and colleagues (2008) investigated a group of patients that received tPA, finding a significant improvement from admission to 24 hour NIHSS, with also a large percentage (94%) of the population showing favorable outcomes at discharge. Kablau, Alonso, Hennerici, & Fatar, (2013)

also found that, in individuals with middle cerebral artery occlusion, those who received tPA exhibited significantly better NIHSS at one week and mRS upon long term follow up compared to those who did not receive tPA.

Some studies indicate that stroke survivors getting tPA have better functional outcomes when initial total scores on the NIHSS reflect a less severe stroke, if they are below the age of 85, and there is an absence of extensive MCA hyperdensity (Albers et al, 2000; Machmumpurath, Reddy, & Yan, 2012). Lower mean arterial BP at the time of onset has also been associated with positive functional outcomes (Albers et al, 2000; Machmumpurath et al, 2012) whereas the presence of aphasia has been found to negatively impact overall recovery after stroke, even in those treated with tPA (Nesi, 2012).

Research also suggests there may be a relationship between severity of stroke, timing of tPA administration, and functional outcomes. Strbian and colleagues (2013) reported that thrombolysis within 90 minutes resulted in better overall outcomes for individuals with moderate stroke, defined as a score between 7-12 on the NIHSS, compared to those with mild or severe stroke, defined as scores of 0-6 or 12 and higher on the NIHSS, respectively. Similary, Nesi and colleagues (2012) found that in individuals with mild stroke, tPA did not have a significant impact on favorable outcomes. In contrast, Kohrmann et al (2009) argues for use of tPA in individuals with mild CVA due to findings of significant improvement after treatment. With the varied evidence, tPA is considered more cautiously if the stroke is rated as ‘mild’ or ‘severe’, based on the NIHSS score.

Thus far, the literature reviewed with respect to the impact of tPA on functional outcomes after ischemic strokes indicates that individuals that receive tPA experience better outcomes providing certain guidelines, such as time of administration, are adhered to. It is also important to point out that the functional outcomes associated with tPA use or its lack of use have only been measured in a general sense with three scales, the NIHSS, Barthel Index, and Modified Rankin Stroke Scale. While these indices provide valuable information relative to basic functions (walking, toileting, eating, and self-care and others) that might be affected by stroke, they do not address changes, for better or worse, in higher level functions such as speech, language, cognition, memory, or executive functions. Minor impairments in these critical areas can be disrupting in a major way in stroke patients in the absence of physical restrictions (Numminen et al., 2016). In addition, most of the studies examining the effects of tPA have assessed outcomes very early, within hours of tPA infusion, or much later, three months of longer after stroke onset.

The next part of this chapter will discuss aphasia after stroke and then current literature regarding tPA and its impact on early speech and language recovery.

Aphasia after Stroke

Aphasia was defined in Chapter 1 as a multi-modal language disorder resulting from damage to the brain's language dominant hemisphere. An estimated 15-30% of individuals that suffer strokes present with symptoms of aphasia at the time of admission to the hospital (Engleter et al, 2006; Inatomi et al, 2008; Laska et al, 2001; Lazar et al,

2010; Maas et al 2012). These symptoms can range from minor word-finding difficulties to near-complete destruction of rule-based semantic, syntactic, and phonological domains of language resulting in Global aphasia. For a small number of stroke patients with aphasia, the symptoms of aphasia disappear within a few hours. For others, aphasic deficits resolve during the spontaneous recovery period (in the first month post-onset) as a result of healing of the damaged brain. But for most patients, the language deficits associated with aphasia persist throughout the acute, subacute, and chronic phases of stroke recovery, and the person's life. (Bakheit et al, 2007; Bersano et al, 2009; Laska et al 2010). Fortunately, aphasia has an improving course. People with aphasia improve their speech and language functioning over time. These improvements are felt to result from several factors according to many neurobehavioral scientists. A summary of the factors considered to impact improvements in speech and language functioning in persons with aphasia follows.

Initial severity of aphasia has repeatedly been shown to be one of the strongest predictors of both short- and long-term language outcomes (Bersano et al, 2009; Chapey, 2008; Kertesz and McCabe, 1977; Hojo et al, 1985; Sarno and Levita, 1979; Plowman, Hentz and Ellis, 2012). This can only be determined after the patient has become neurologically stable and the life-threatening consequences of stroke have been dealt with by the medical team (Brookshire, 2015). In general, for patients with aphasia who are considered to be neurologically stable, individuals with more severe language deficits at stroke onset have poorer outcomes compared to those with milder impairments. Severity of aphasia and speech and language improvement in patients with aphasia has also been found to be influenced by the site and extent of the causative lesion or lesions caused by

the stroke (Kertesz, 1979; Kertesz & McCabe, 1977; Knopman, Selnes, Nccum & Associats, 1984, 1985; Rubens, 1977) as well as the extent to which the brain damage that causes aphasia disrupts connections between areas of the brain's left hemisphere important to language processing (Hillis et al, 2000; Kertesz, 1979).

The role of age on speech and language outcomes for stroke patients with aphasia appears to be equivocal. Some researchers have found older patients have poorer language outcomes (Chapey, 2008; Ogrezeanu et al, 1994) while others report no relationship between age and improvement in language functioning in aphasia (Basso, 1992; de Riesthal and Wertz, 2004). However, individuals with advanced age, specifically over 65, have a higher chance of institutionalization after stroke (Edwardson & Dromerick, 2017; Koennecke et al, 2011; Konig et al, 2008; McClung, Gonzalez Rothi, & Nadeau, 2010; Plowman et al, 2012; Ross & Wertz, 2001), which would negatively impact opportunities for communication and potentially impact language improvement.

Other demographic factors should be mentioned relative to their impact or lack of impact on aphasia outcomes. Gender has been found to be equivocal as a significant predictive factor for aphasia recovery with some authors concluding that females have poorer outcomes (Holland, Greenhouse, Fromm, & Swindoll, 1989) and others finding males with poorer outcomes (Sarno & Levita, 1979). Similarly, while many have studied it, the impact of level of education on general stroke outcomes is inconclusive (Connor et al, 2001; Lazar et al, 2008; Ross & Wertz, 2001; Smith, 1971; Benjamin et al, 2017).

Patient complexity is often determined by the presence of concurrent medical problems, or co-morbidities. Individuals with fewer co-morbidities along with their aphasia have shorter lengths of stay and better recovery (Holland et al, 1989; Marshall & Phillips, 1985). Another indicator of patient complexity is the need for polypharmacy, defined as more than five medications. Certain medications can even have a negative impact on functional recovery (Goldstein, 1995; Goldstein, 1998) after stroke. Therefore, polypharmacy at the time of stroke and during recovery may be a contributing factor to the success of aphasia rehabilitation.

Speech and Language Improvement after tPA

As evinced in the material that has been reviewed so far, a myriad of factors influences overall recovery of speech and language skills after left hemisphere stroke. Early recovery, however, within the acute phase, is often driven by spontaneous recovery, associated with improvements in language skills by patients with aphasia without therapeutic intervention. These improvements result from reduced swelling, increased blood flow, resolution of psychological shock, and lessening of diaschesis associated with healing of the brain (Kertesz & McCabe, 1977; Rubens, 1977; Wepman, 1972). Two phases of spontaneous recovery have been recognized, early and late. The early phase begins as soon as the 2nd or 3rd day post onset (Rubens, 1977) and continues for approximately 2 weeks (Pashek & Holland, 1988; Pederson, Jorgensen, Nakayama, Raaschou, & Olson, 1995). Consequently, within the first several days post ictus, patients with aphasia are highly variable. Daily fluctuation makes accurate assessment difficult. Tissue reperfusion within the early days post stroke can also be influenced by completed

procedures such as carotid endarterectomy and stenting, induced blood pressure changes, and other methods of spontaneous reperfusion (Hillis & Heidler, 2002). In the first week, with non-thromoblized patients, location of infarct, age, and maintenance of blood pressure are also significant factors in early aphasia recovery (Muscari et al, 2013).

There is consensus that these changes start early and the majority of spontaneous recovery continues for several weeks after the insult (Culton, 1969; El Hachioui et al, 2012; Hillis and Heidler, 2002; Pederson et al, 1995). Persons with aphasia can have significant gains within the first few months, even in the absence of ongoing speech and language therapy (Culton, 1969; Hartman, 1981). One of the more informative studies on spontaneous recovery was completed by Pederson and colleagues in 1995, in which investigators completed weekly assessments on 330 persons with aphasia and found 84% and 95% of the sample exhibited stationary language improvement at two and six weeks post onset, respectively. This is a substantial gain, especially considering no therapy to address impairments. El Hachioui (2012) found similar patterns of early recovery across a sample of 147 persons with aphasia at weekly intervals, irrespective of whether they received any aphasia therapy, suggesting considerable reliance on the process of spontaneous recovery. However, the impact of tPA on speech and language skills during this spontaneous recovery phase is not definitively provided in the current literature.

Research specifically addressing recovery of speech and language deficits after thrombolysis consists of case studies, retrospective analyses, and studies using subjective rating scales as outcome measures. Few prospective, group studies provide evidence of the impact of tPA on specific speech and language tasks. Several case studies report significant improvement of language deficits in individuals of varying age and severity,

even full recovery at times (Cho, Hermier, & Nighoghossian, 2015; Mazza, 2012; Mehrpour, Motamed, Aghaei, Jalali, & Ghoreishi, 2014; Sontineni, Mooss, Andukuri, Schima, & Esterbrooks, 2009). One of the only investigations using a standardized speech and language measure was a case series by Finch et al in 2014, in which four individuals who received tPA were measured at two weeks and again at three months with the Western Aphasia Battery (WAB) and a Motor Assessment Scale. In these cases, authors were unable to detect any reliable change in language function related to the tPA.

Restrospective group studies, the majority of which use the NIHSS to measure speech and language changes, overall suggest good recovery of deficits with administration of tPA. One retrospective study investigated only individuals who had aphasia present and compared the NIHSS and mRS scores at the end of an inpatient rehabilitation program for those who did and did not receive tPA. With 37 individuals in each group, the tPA group scored significantly higher at the end of a rehabilitation program on these scales compared to their counterparts who did not receive tPA (Meiner et al, 2010), with authors concluding that tPA has a significant impact on speech and language recovery. Another study looked specifically at a group of more than 600 individuals with isolated aphasia as defined by the aphasia subscale of the NIHSS, all of whom received tPA (Lundstrom, Zini, Wahlgren, & Ahmed, 2015). This study retrospectively analyzed the NIHSS scores at seven days and the mRS scores at three months, finding that almost half of the population resolved by one week and the vast majority (86%) were functionally independent by three months. Therefore, authors report that persons with isolated aphasia, in the absence of other physical impairments, may respond more readily to medical treatments, such as tPA.

In one of the few retrospective group studies using a standardized aphasia assessment, Jacquin and colleagues (2014) considered Boston Diagnostic Aphasia Examination (BDAE) scores at one week and three months after stroke to compare one cohort of subjects who received tPA to one group that did not. Authors reports improvement in speech and language after tPA because a significant difference was observed in scores between the thrombolyzed individuals and the non-thrombolyzed individuals at both time points.

One additional retrospective study used the BDAE scores, in addition to the Lisbon Aphasia Assessment Battery and a created Composite Verbal Score (CVS), including subscale scores on the NIHSS (Martins et al, 2017). This analysis included only individuals with a left MCA infarct who received tPA. Results indicated that 31% of individuals with aphasia had complete recovery and 72% had some recovery after tPA on day seven (Martins et al, 2017). Authors also found significant correlation between the CVS and the standardized measures in this study, suggesting that use of this novel scale can be used to predict improvement on objective tasks.

Prospective studies specifically investigating early speech and language deficits after tPA are limited and have used the NIHSS and other subjective scales as a primary outcome measure. In 2012, Maas and colleagues used the NIHSS to investigate changes in those with aphasia starting in the 'hyperacute' window, defined as 12 hours after stroke. The aim of the study was to examine the prognosis of aphasia in a group of 204 individuals, 60 of whom received tPA. Of the 60, authors found that from baseline to six months 86% improved, defined as any decrease in language score on the NIHSS and 73% resolved symptoms, defined as a language score of zero on the NIHSS. Investigators in

this study concluded that tPA is an effective treatment to significantly improve speech and language skills.

Another study used similar guidelines to define 'improvement' based upon changes in the NIHSS language score (Kremer, Perren, Kappelin, Selariu, Abul-Kasim, 2013). In 50 individuals with aphasia who received tPA, authors found that 16% of the group improved in their aphasia score at 24 hours after stroke onset; however, this was not a statistically significant finding. At 24 hours, 46% of the population demonstrated global improvements. Authors also found a significant correlation between infarct volume on CT scan and aphasia score, suggesting size of lesion as a significant factor in functional impairment. Additionally, the difference in individuals with improved aphasia at three months was not significant in this study.

A recent prospective study (Denier et al, 2015) used the NIHSS to measure change in the first week after stroke. All participants in this study received thrombolysis and authors created two measures using the NIHSS subscales: a composite language score and a composite motor score. Of the 338 individuals who received tPA, 137 had aphasia. The NIHSS was used to record aphasia scores at baseline, 24 hours, and day seven. The individuals with aphasia in this study also received daily speech and language therapy if appropriate. Of these, 10% demonstrated what the authors called a 'dramatic recovery'. The individuals with aphasia and no associated limb deficits who received tPA had significantly better aphasia outcomes compared to those with limb deficits. Further analysis of this data set (Denier, 2016) analyzed individuals with isolated aphasia and showed that compared to those who did not receive tPA, the individuals who did

performed significantly better on the NIHSS, composite language score, and the LAST screening at one week after stroke.

In summary, current literature suggests improvement of speech and language skills when tPA is used as a treatment after stroke. However, data are variable and suggest that improvement may not happen in the early post onset period. Research also indicates that individuals with isolated aphasia may respond more readily to tPA treatment compared to those with strokes characterized by more comprehensive deficits. Measures used thus far in studies have primarily been subjective scales, which may not provide a comprehensive picture of impairment or specific changes in skills (Finch, Hayward, Fleming, & Copland, 2013).

This study aims to address continued questions about the response of speech and language skills to the use of thrombolysis and the lack of prospective studies using specific speech and language tasks, especially during the spontaneous recovery phase. The goal is to gather more descriptive and prognostic information about what early speech and language recovery looks like for those individuals who do and do not receive this neuro-protective intervention. Our patients are changing significantly during the time required for the SLP to make decisions about prognosis and rehabilitation needs. It is imperative for acute care SLPs to have more data on the progression and prognosis of individuals with aphasia after a stroke, with and without other medical interventions, to help inform best practice, patient education, and resource management within the hospital.

Chapter Three- Methodology

Purpose

The purpose of this study was to examine early speech and language changes in survivors of a first-ever stroke with aphasia who did and did not receive tPA. To do this, a prospective observational design was utilized. The study was approved by the University of Kentucky Office of Research Integrity and Institutional Review Board (Protocol # 15-0066-P1H).

Participant Recruitment

To participate in the study, subjects were required to meet the following inclusion criteria: 1) diagnosis of a unilateral left hemisphere ischemic stroke with aphasia, 2) right handed, 3) no prior strokes, 4) age minimum of 18 years old, 5) no other neurological diagnoses that may have resulted in speech and language impairments, and 6) Native English speaker. No upper age limit was utilized.

Between April 2015 and October 2017, a total of 627 patients admitted with a diagnosis of stroke to the University of Kentucky Medical Center were screened for possible inclusion in the study. Screening was completed by the primary investigator or a trained research assistant. This was a convenience sample, as the investigator had direct clinical access to these patients and was a member of the stroke assessment team. However, not all consecutive stroke admissions were able to be screened due to limitations in the investigator's schedule. Of the 627 potential participants screened, 432

had a left hemisphere ischemic stroke. Figure 3.1 shows that of this number, 32 patients were originally considered to have met inclusion criteria. All of these individuals were asked to give informed consent for participation within the first 24 hours after their stroke. If the primary investigator determined a subject to have impaired consent capacity, as approved by the IRB, consent was obtained from a Legally Authorized Representative (LAR). Four of the 32 subjects meeting selection criterion did not participate in the study; two of the individuals thought to have met inclusion criteria were found not to have had strokes and were eventually ruled out; two subjects refused to participate. Of the remaining 26 subjects who gave consent, 13 received tPA and 13 did not. The administration of tPA was solely the decision of the admitting neurologist(s) and made before the participant gave consent to participate in the study. Table 3.1 provides background, demographic, and medical information on each participant who did and did not receive tPA. For the entire sample, the mean age was 70.7 years (Standard deviation: 13.3; Range: 46-93). The National Institute of Health Stroke Scale (NIHSS), as a measure of stroke severity, was available on each participant both upon admission and at twenty-four hours after stroke. The mean NIHSS total score at time of admission for the group was 10.8 (Standard deviation: 5.9; Range: 1-20).

Procedures/Measures

After informed consent was obtained, each subject was briefly interviewed by the primary investigator to establish rapport and was administered simple vision and hearing screening tests to ensure validity of data collection. When a participant could not respond

verbally, hearing was screened using an oto-acoustic emission (OAE) device, requiring no direct response from the participant. If the participant was verbal, hearing was screened using the CID Everyday Speech Sentences (Davis and Silverman, 1978). Vision was screened with a modified version of a word scanning/cancellation task (Beukelman & Mirenda, 1998). See Appendices A and B for hearing and vision screening tools.

Participants were scheduled to be assessed four times during the course of the study with four objective tasks (1) forward digit repetition (FDR), (2) polysyllabic word repetition (PWR), (3) picture description (PD), and (4) picture naming (PN). These tasks were selected because they are commonly used by speech language pathologists to assess speech and language abilities of individuals with aphasia in acute hospital settings, contain few materials, are convenient to use in clinical environments, contain relatively straight-forward instructions, and are easily recorded by audiotape for later scoring and analysis. These tasks are briefly described in the following paragraphs. Details on the materials, instructions, administration, and scoring of each task are provided in Appendices C, D, E and F.

Forward Digit Repetition (FDR): The FDR task was used to assess the participant's short term and working memory skills. This task required the subject to repeat five sets of 5, 6, and 7-digit strings after the examiner. The subject was credited for digit produced in the correct location of the digit string.

Polysyllabic Word Repetition (PWR): For the PWR task, the subject repeated 10 polysyllabic words one-at-a-time after the examiner from a protocol developed by Rosenbek and colleagues (Rosenbek, Wertz, & LaPointe, 1989). This task was used to

confirm the presence and severity of apraxia of speech, a neuromotor speech disorder often co-occurring with aphasia (Wambaugh & Shuster, 2008).

Picture Description (PD): Two pictures, the "Picnic Scene" from the revised Western Aphasia Battery-Revised (WAB-R; Kertesz, 2006) and the "Cookie Theft" picture from the Boston Diagnostic Aphasia Examination-3 (BDAE-3; Goodglass, Kaplan, & Barresi, 2000) were used to obtain a connected speech sample from each subject. Both tasks have been used successfully in several studies to assess connected speech abilities of persons with aphasia and have high reliability and good validity (Golper, Thorpe, Tompkins, Marshall, & Rau, 1980; Nicholas & Brookshire, 1995; Yorkston & Beukelman, 1981). These discourse samples were used to calculate correct information units and words per minute. Correct information units provide a measure of word retrieval in discourse, specifically assessing informativeness and efficiency of communication. Words per minute provide a measure of verbal fluency and rate of speech.

Confrontational Picture Naming (PN): Stimuli from the short forms of the Philadelphia Naming Test (PNT: Walker & Schwartz, 2012) were used to develop four separate 10-item picture naming tasks. Pictures for each task were selected so as to adhere to the word frequency distributional properties of the original PNT. Pictures were presented for naming one-by-one without cues or prompts.

Table 3.2 shows the location where assessments took place for each participant within 24 hours of stroke onset, 1 week, 2 weeks, and 3 months post-onset. The 24 hour assessment was conducted in the acute care hospital for all participants. Subsequent

assessments took place in either the acute care hospital, rehabilitation hospital, or participant's home depending on where the participant was located at that assessment. The four objective tasks were administered to participants in the same order-FDR, PWR, PD, and PN- at the four assessments. The primary investigator was responsible for all evaluations, which lasted approximately 20 minutes and were completed in a quiet, well-lit environment. To ensure consistency by the primary investigator across assessments, a script for data collection was utilized. See Appendix G for script/procedures. To limit frustration from the participant, no prompting or cues were provided during data collection. Since all assessment tasks required verbal responses and the examiner's scoring of responses would lengthen testing time, subjects' responses were audiotaped and scored at a later time. In addition, out of consideration of the fact that participants were in acute stages receiving intensive medical care, precautions were taken to terminate administration of a dependent measures if the subject became frustrated, failed repeatedly, or could not perform a task (See Appendices). An additional measure, the Stroke and Aphasia Quality of Life Scale-39 was also included as part of the 3 month post-onset assessment.

Stroke and Aphasia Quality of Life-39 (SAQOL-39): This self-assessment scale was scheduled to be administered only at the three-month assessment because it was anticipated subjects would no longer be in a hospital at this time and earlier assessments took place too early to provide self-reports on quality of life after stroke. The SAQOL-39 measures health-related quality of life in four sub-domains after stroke: physical, psychosocial, communication, and energy. The scale has been found to demonstrate good acceptability, internal consistency, test-retest reliability, and construct validity (Hilari,

Byng, Lamping, & Smith, 2003). These psychometric properties also apply when the SAQOL-39 is administered by proxy and via telephone (Hilari, Owen, & Farrelly, 2007; Caute, Northcott, Clarkson, Pring, & Hilari, 2012). See Appendix H for a copy of the SAQOL-39. When possible, the SAQOL-39 was given directly to the person with aphasia. However, in some cases, the measure was completed by proxy to a close family member who lived with the participant. The overall score and the scores for each domain were calculated. In analysis, the overall score, communication score, and psychosocial score were used.

Demographic, Medical, and Speech-Language Therapy Data

Demographic, medical, and speech and language data were obtained for each participant. Most of these data were obtained at the start of the study and entered on the data collection forms shown in Appendices I.1-4. Much of the demographic and medical information was obtained from the medical record, patient, or family report. This included contact information, date of birth, level of education, location of stroke in the brain, tPA administration information, medications, co-morbidities, ambulation status, and ongoing National Institute of Health Stroke Scale (NIHSS) scores assigned by medical personnel. After informed consent was given, this information was entered on the data collection forms.

Demographic information included the subject's age (in years), gender (male or female), and highest level of education (elementary school, middle school, high school, technical school, bachelor's degree, and post-bachelor's degree). Medical data included the subject's overall and language scores on the National Institute of Health Stroke Scale

(NIHSS), weighted score on the Charleston Comorbidity Index (CCI; deGroot, Beckerman, Lankhorst, & Bouter, 2001), and a polypharmacy designation of "plus" or "minus" based on the number of medications the individual was taking.

The National Institute of Health Stroke Scale (NIHSS) is a clinical tool used by many neurologists and stroke unit nurses to measure level of impairment after a stroke and to document changes in stroke severity in the short- and long-term. The NIHSS has 11 items, including the following domains: level of consciousness, gaze, visual, facial palsy, motor arm, motor leg, limb ataxia, sensory, language, dysarthria, and neglect. Each item has a graded scoring system of 0-3 or 0-4, with a total summed score varying from 0-42; a higher score reflects a more severe impairment. See Appendix K for a copy of the NIHSS. In this study, the NIHSS was scored by physicians and nurses as part of standard stroke unit care. Both the total and language scores were recorded by the investigator from the medical record. To maintain consistency across participants, admission scores were recorded from the history and physical document, which was completed by the physician. The 24 hour NIHSS scores, however, were not always scored by the physician and were therefore recorded from the nursing flowsheets.

Comorbidities (associated health problems) provide an indication of the individual's pre-stroke health status, which may impact overall recovery. For this study, this was determined using the Charlson Comorbidity Index (CCI). The CCI index was originally validated on a large study population that included patients with stroke (deGroot, Beckerman, Lankhorst, & Bouter, 2001) and has been used in stroke outcome studies (Goldstein, Samsa, Matchar, & Horner, 2004). A patient's score on the CCI represents a sum of assigned weights for specific diagnoses. See Appendix J for a list of

included diagnoses and weights. CCI scores for each participant in this study were determined from a review of diagnoses listed in the note when the patient was admitted to the acute care hospital.

Another measure of patient complexity is the number of medications prescribed. To determine the risk of polypharmacy for each participant, a simple count of the number of medications ordered during hospitalization was made. The median number of medications taken by study participants was 10. Therefore, participants who had more than 10 medications were coded as positive (+) for polypharmacy and those with fewer were coded as negative (-) for polypharmacy.

For those participants completing the three-month assessment, the amount of speech and language intervention was calculated based on number of hours of therapy. By the time of their third assessment (2 weeks) most of the participants had been sent home, to a rehabilitation hospital, or to a long term care facility. Between the time of the 2 week and 3 month assessments, most participants received varying amounts of formal speech and language therapy. Since the amount of speech and language therapy a patient with aphasia receives influences recovery, the total number of formal speech and language hours was calculated for each patient from 24 hours to 3 months.

Reliability and Validity

Several steps were taken to minimize bias. All dependent measures were given by the primary investigator using a script to ensure consistent presentation of instructions. Subjects' responses to each task were audio recorded and then scored by an independent

listener. For the FDR, PWR, and PD, a trained research assistant completed all scoring. To calculate information units (IUs), both the research assistant and investigator completed extensive training and were required to demonstrate competency in calculating IUs prior to data scoring. Inter-rater reliability testing was completed on 10% of participant responses for each outcome measure.

Data Analysis

Data for analyses were entered in an Excel database and imported into Statistical Package for the Social Sciences (SPSS). All statistical analyses were performed using SPSS v18. Independent two-sample t tests were used for group comparisons on demographic and medical variable measures. Repeated measures multivariate analysis of variance (MANOVA) was used to analyze the within- and between- subjects effects of time and group on mean scores on the speech and language measures. Independent two-sample t tests were used post hoc to investigate individual differences between tPA/non-tPA group means. All measures were tested for normality with Shapiro-Wilks tests. Data sets were observed to be normally distributed and parametric tests were used. Finally, correlational analyses and linear regression analysis were completed to investigate relationships between dependent measures and other variables. In agreement with the sample size analysis completed a priori, an alpha of 0.1 was chosen to detect significance.

Figure 3. 1: Study Recruitment

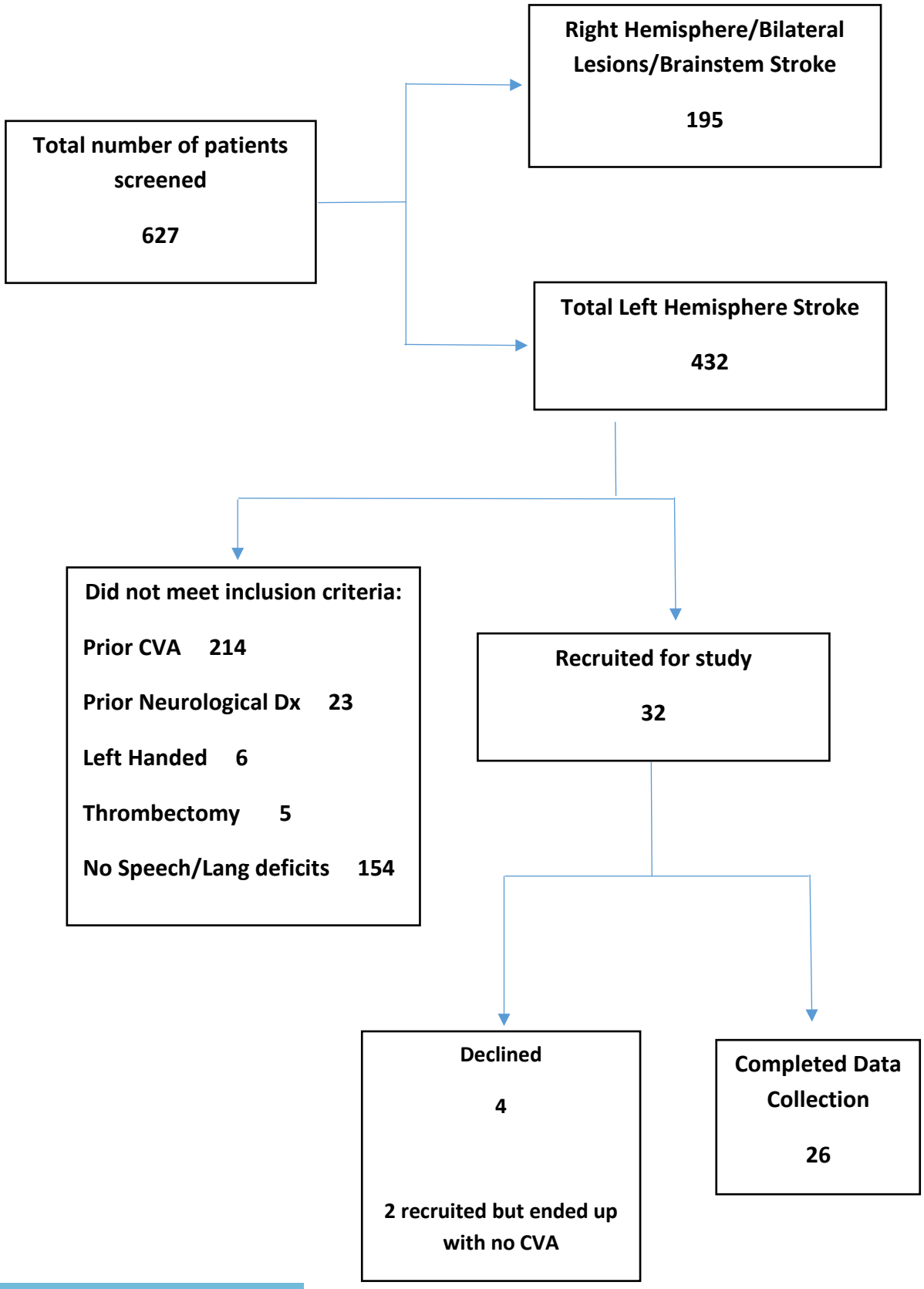


Table 3. 1

Demographic and medical variables on participants who received tPA (n=13)

Sub	Age	Gender	Education	Lesion Location	CCI *	Polypharmacy (+/-)	NIHSS Total Admission
1	81	Male	High School	Left MCA	0	-	4
2	93	Female	High school	Left M1 branch	0	-	14
3	69	Male	Technical School	Left frontal lobe	0	-	10
4	53	Male	College	Left insular cortex	0	+	20
5	83	Female	Technical School	Left thalamus, BG	1	-	7
6	66	Male	Middle School	Left MCA	0	-	13
7	61	Male	College	Left MCA	0	-	18
8	74	Male	High school	Left frontoparietal	2	-	6
9	46	Male	High school	Left temporal lobe, BG	0	-	15
10	67	Female	High school	Left parietal lobe	1	+	18
11	85	Male	Unknown	Left MCA	3	+	16
12	77	Male	High school	Left MCA	0	+	7
13	49	Male	High school	Left MCA	0	-	12

*Charlson Comorbidity Index

Demographic and medical variables on participants who did not receive tPA (n=13)

Subject	Age	Gender	Education	Lesion Location	CCI *	Polypharmacy (+/-)	NIHSS Total Admission
1	81	Male	Middle School	Left thalamus	1	+	14
2	63	Female	Middle School	Left frontal lobe	1	+	5
3	59	Female	College	Left internal capsule	3	+	2
4	60	Female	College	Left MCA	0	-	15
5	85	Female	Elementary School	Left occipital lobe	0	-	12
6	82	Female	High school	Left temporal and parietal lobes	0	-	4
7	77	Male	Post graduate	Left MCA	0	-	8
8	86	Male	Elementary School	Left MCA	5	-	18
9	57	Female	College	Left parietal	1	-	6
10	64	Male	Middle School	Left MCA	0	+	13
11	74	Female	College	Left MCA	0	+	1
12	56	Male	High school	Left MCA	3	+	20
13	90	Female	High school	Left MCA	0	+	3

*Charlson Comorbidity Index

Table 3. 2
Assessment locations for individuals who received tPA (n=13)

PARTICIPANT	24 HOUR ASSESSMENT	1 WEEK ASSESSMENT	2 WEEK ASSESSMENT	3 MONTH ASSESSMENT
1	ACH	ACH	RH	NA
2	ACH	ACH	ACH	H
3	ACH	ACH	RH	NA
4	ACH	H	H	H
5	ACH	H	H	NA
6	ACH	ACH	ACH	NA
7	ACH	ACH	RH	H
8	ACH	H	H	H
9	ACH	OP	OP	H
10	ACH	ACH	ACH	NA
11	ACH	ACH	ACH	NA
12	ACH	H	H	H
13	ACH	OP	OP	NA

ACH- Acute Care Hospital; RH- Rehabilitation Hospital; OP- Outpatient Clinic; H- Participant's Home; NA- Assessment not completed

Assessment locations for individuals who did not receive tPA (n=13)

PARTICIPANT	24 HOUR ASSESSMENT	1 WEEK ASSESSMENT	2 WEEK ASSESSMENT	3 MONTH ASSESSMENT
1	ACH	ACH	RH	NA
2	ACH	H	H	H
3	ACH	H	H	NA
4	ACH	ACH	RH	OP
5	ACH	ACH	RH	NA
6	ACH	ACH	RH	NA
7	ACH	ACH	RH	NA
8	ACH	ACH	ACH	NA
9	ACH	H	H	NA
10	ACH	ACH	RH	NA
11	ACH	ACH	H	H
12	ACH	ACH	RH	H
13	ACH	H	H	H

ACH- Acute Care Hospital; RH- Rehabilitation Hospital; OP- Outpatient Clinic; H- Participant's Home; NA- Assessment not complete

Chapter 4- Results

This chapter begins with a summary of the analyses carried out to determine the appropriate sample size for the study followed by a brief description of the methods used to determine inter-rater reliability in scoring. This is followed by a set of analyses designed to answer the primary research questions posed for the study, investigating changes in speech and language in the acute phase of stroke recovery. The final segment in this chapter explains results of the secondary research question, investigating the relationship between performance on speech, language, and quality of life measure, and various demographic, medical, and therapeutic variables.

Sample Size Analysis

To assess for an adequate sample size, an a priori analysis was completed using one of the outcome measures for the study, percent correct information units. This outcome measure was chosen because it provides an overall picture of a participant's word retrieval in connected speech. Based on pilot data (Boyle, 2014; Gordon, 2008), the investigator expected the mean percentage of correct information units in a language sample to be 0.5 (50%) for participants after a left hemisphere stroke not receiving tPA, with a standard deviation of 0.15 (15%). Further, the mean percentage was estimated to be 0.65 in subjects receiving tPA. Using a two-sided test with a 0.1 significance level, due to the pilot nature of this trial, a minimum of 13 participants per trial arm were required to have 80% power to detect this difference in the means.

Scoring Reliability

To ensure accuracy in scoring responses, inter-scorer reliability was calculated for each outcome measure. Ten percent of responses at each assessment were randomly selected for reliability checking. For FDR, %IUs, and WPM, responses were scored by a trained research assistant and re-scored by the primary investigator. For PWR, scoring was completed by the primary investigator and re-scored by an independent SLP. For the PN task, scoring was completed by an independent SLP and re-scored by the primary investigator. Inter-rater reliability was calculated using the following formula: [the total number of agreements/ the total number of possible agreements] x 100. An a priori level of 90% agreement was deemed adequate for the study. Reliability testing revealed agreement of 100% for FDR, 91% for PWR, 91.6% for %IUs, 91.6% for WPM, and 98% for PN.

Research Questions

Primary Questions

The three primary questions in this study investigate the differences in speech and language recovery and quality of life over various assessment points in individuals after first-ever left hemisphere stroke. The first question investigates the recovery of the entire sample of individuals, regardless of whether they received neuroprotective intervention during a two-week timeframe, with assessments at 24 hours, 1 week, and 2 weeks post stroke. The second question evaluates the differences between two groups- those who

received tPA and those who did not- at the same assessment points. The third question assesses the differences on speech and language tasks and a quality of life measure at three months between those who received tPA and those who did not, all of whom had received some speech and language therapy at the three month assessment.

Question 1: Do persons with aphasia following a first-ever left hemisphere ischemic stroke improve speech and language skills in the first two weeks post onset?

Table 4.1 gives the means and standard deviations for the Forward Digit Repetition (FDR), Polysyllabic Word Repetition (PWR), Picture Naming (PN), and the two measures associated with Picture Description, percent information units (%IU), and words per minute (WPM) for the 24 hour, 1 week, and 2 week assessments. These data pertain to all 26 subjects irrespective of tPA status and hence provide an indication of language changes in the acute phase of stroke recovery. To address research question 1, a repeated measures multivariate analysis of variance (MANOVA) was carried out for each of the aforementioned outcome measures to examine differences in scores over time. Table 4.1 shows that statistically significant gains were evinced on all of the language tasks examined over the first two weeks post onset. Subsequent pair-wise comparisons to examine changes on each measure from 24 hours to 1 week, 1 week to 2 weeks, and 24 hours to 2 weeks revealed that changes were significant for all measures from the 24 hour to the 1-week evaluation and from the 24 hour to the 2-week evaluation. Pair-wise comparisons from the 1 week to the 2-week evaluation approached significance for the FDR task and reached significance for the objective indices associated with the PD task as reflected by the scores for the %IU and WPM measures. These results are in agreement with several studies that have documented relatively robust improvements in

speech and language in patients with aphasia in the early post onset period, a time when many patients are undergoing spontaneous recovery (Culton, 1969; Hartman, 1980; Pederson et al, 1995). While the present study corroborates earlier findings, it also provides evidence that spontaneous recovery begins quite early and can be objectively measured in acute ischemic stroke patients with aphasia.

Table 4. 1 Mean scores, (standard deviations), and p values for all participants (n=26) for Forward Digit Repetition (FDR), Polysyllabic Word Repetition (PWR), Percent Information Units (%IUs), Words Per Minute (WPM), and Picture Naming (PN) for the 24 Hour, 1 Week, and 2 Week Assessments

Measure	24H (1)	1 WEEK (2)	2 WEEK (3)	Sig.	1 to 2	2 to 3	1 to 3
FDR	37.2 (40.6)	52.2 (41.3)	61.6 (37.5)	*p*=.00*	*p*=.03*	*p*=.12	*p*=.00*
PWR	1.9 (1.7)	3.1 (1.7)	3.2 (1.7)	*p*=.00*	*p*=.00*	*p*=.21	*p*=.00*
%IUs	23.6 (32.6)	36.1 (37.6)	52.4 (37.6)	*p*=.00*	*p*=.08*	*p*=.04*	*p*=.00*
WPM	28.1 (29)	35.7 (31.3)	44.9 (34.4)	*p*=.01*	*p*=.02*	*p*=.08*	*p*=.01*
PN	37.6 (40.3)	59.2 (40.4)	58.8 (42)	*p*=.00*	*p*=.00*	*p*=1.0	*p*=.01*

*alpha 0.10

Question 2: Do persons with aphasia following a first-ever left hemisphere ischemic stroke who do and do not receive tPA exhibit differences in speech and language recovery in the first two weeks post onset?

This question addressed the possibility that the restoration of blood flow through administration of tPA to a stroke survivor with aphasia might result in better speech and language outcomes as compared to individuals not receiving tPA. Before examining any differences in language performance between participants who did (n = 13) and did not (n=13) get tPA, however, independent two sample t-tests were used to explore the possibility that the groups might differ on selected variables that could potentially impact speech and language outcomes. Table 4.2 shows the means and standard deviations for

the two groups for age and educational level, scores for the Charlson Comorbidity Index, polypharmacy, NIHSS stroke scale, and NIHSS language scale (at admission and at 24 hours). None of the two sample t-tests supported differences between the groups for any of the variables shown in Table 4.2. It does appear, however, that overall scores of stroke severity and language subscale scores on the NIHSS made by neurologists and/or nurses reflected that initially, the tPA group sustained more severe strokes. Additionally, for the discourse task, it is important to note that percent information units can be impacted by the total number of words produced by the individual. For this reason, the total number of words for each participant on this task at each assessment was calculated and no significant differences between groups were observed.

Table 4. 2 Means, standard deviations, and p values of demographic, medical, and therapeutic variables for participants who did receive tPA (n=13) and who did not receive tPA (n=13)

Variable	Group	Mean	SD	*p value*
Age	tPA	69.5	14.5	.67
	Non-tPA	71.8	12.4	
Education	tPA	2.4	.9	.85
	Non-tPA	2.3	1.7	
Comorbidity Index (CCI)	tPA	.5	.9	.31
	Non-tPA	1.1	1.6	
Polypharmacy *(% positive)*	tPA	.3	.5	.25
	Non-tPA	.5	.5	
NIH Total Admission *(Possible score: 0-42)*	tPA	12.3	5.2	.19
	Non-tPA	9.3	6.4	
NIH Total 24 Hours *(Possible score: 0-3)*	tPA	9.8	7.1	.39
	Non-tPA	7.5	5.7	
NIH Lang Admission *(Possible score: 0-42)*	tPA	2.1	.8	.58
	Non-tPA	1.9	.6	
NIH Lang 24 Hours *(Possible score: 0-3)*	tPA	1.8	.7	.43
	Non-tPA	1.6	.7	

*alpha 0.10

A repeated measures MANOVA was utilized to answer Question 2 and investigate the interaction of a within-subjects factor of time with a between-subjects factor of tPA. Results, as indicated in Table 4.3, show that for four of the five outcome measures (PWR, %IUs, WPM, PN), there was no significant effect of tPA or interaction between time and tPA. For FDR, there was a significant interaction of time and tPA detected at p=.08. Post hoc independent two sample t tests were used to analyze between-subject group differences for this measure, revealing no significant group differences at any of the three assessments [24 Hour (p=.69), 1 week (p=.79), 2 week (p=.34)].

Table 4. 3 ***p* values for MANOVA on each outcome measure across assessments at 24 Hours, 1 Week, and 2 Weeks for all participants (n=26)**

Measure	Time p value	tPA *p* value	Time*tPA *p* value
FDR	.00*	.55	.08*
PWR	.00*	.71	.11
%IUs	.00*	.65	.79
WPM	.01*	.99	.37
PN	.01*	.21	.54

*alpha 0.10

Because the MANOVA did not reveal any significant group differences, mean scores are provided as additional descriptive information. Table 4.4 shows the mean scores and standard deviations for each of the five outcome measures for the 24 hour, 1 week, and 2 week assessments for the groups who did and did not receive tPA. The means for both groups align with the results for Question 1, revealing improvements made from 24 hours to 2 weeks, regardless of tPA status. A visual representation of changes over time by each group is provided for FDR (Figure 4.1), PWR (Figure 4.2),

%IUs (Figure 4.3), WPM (Figure 4.4), and PN (Figure 4.5). As seen in these graphs, for FDR, PWR, and WPM, group means were variable and the non-tPA group actually exhibited the same or higher scores compared to the tPA group at some assessments. However, for the %IUs and the PN tasks, the tPA group consistently performed better at every assessment. To provide additional descriptive information about the participants' performance on these speech and language tasks, the mean amount of change for each group was also calculated for each measure, as reflected in Table 4.5. For the mean scores on all measures, it is also important to highlight that during the first two weeks, the standard deviations around the means are very large for both groups, emphasizing the large variability in performance within the sample.

Table 4. 4 **Mean scores and standard deviations for participants who did receive tPA (n=13) and who did not receive tPA (n=13) for Forward Digit Repetition (FDR), Polysyllabic Word Repetition (PWR), Percent Information Units (%IUs), Words Per Minute (WPM), and Picture Naming (PN) for the 24 Hour, 1 Week, and 2 Week Assessments**

Outcome measure	Group	Mean	SD
FDR 24 Hours	tPA	27.7	37.8
	Non-tPA	35	42.2
FDR 1 Week	tPA	55.3	40.3
	Non-tPA	50.2	43.6
FDR 2 Weeks	tPA	55.4	37.8
	Non-tPA	59.4	37.8
PWR 24 Hours	tPA	1.9	1.9
	Non-tPA	1.6	1.7
PWR 1 Week	tPA	2.8	1.9
	Non-tPA	3.1	1.7
PWR 2 Weeks	tPA	3.2	1.8
	Non-tPA	3.2	1.5
% IUs 24 Hours	tPA	24.4	33.8
	Non-tPA	15.6	28.8
% IUs 1 Week	tPA	40.2	36.3
	Non-tPA	34.9	39.8
% IUs 2 Weeks	tPA	55.4	34.8
	Non-tPA	42.4	39.3
WPM 24 Hours	tPA	29.8	32.7
	Non-tPA	21.3	22.9
WPM 1 Week	tPA	34	35.5
	Non-tPA	34.3	25.3
WPM 2 Weeks	tPA	46.2	38.1
	Non-tPA	43.1	26.2
PN 24 Hours	tPA	42.5	43.3
	Non-tPA	21.5	34.1
PN 1 Week	tPA	70	38.4
	Non-tPA	42.9	38.9
PN 2 Weeks	tPA	69.6	37.9
	Non-tPA	40.9	40.6

Figure 4.1- FDR

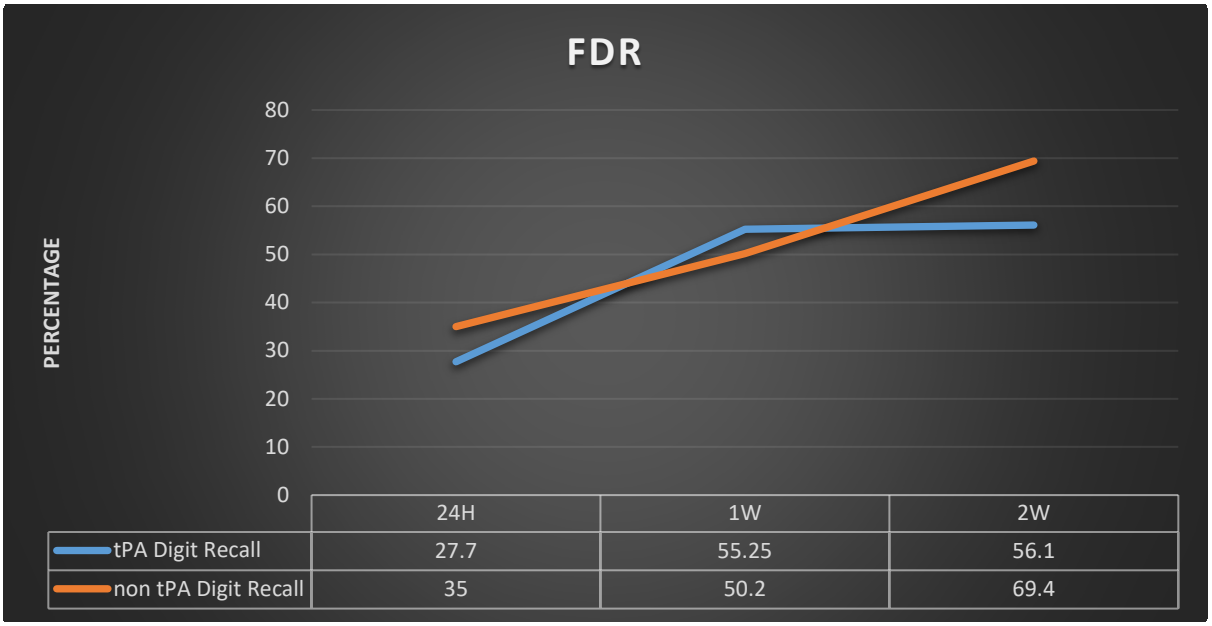


Figure 4.2- PWR

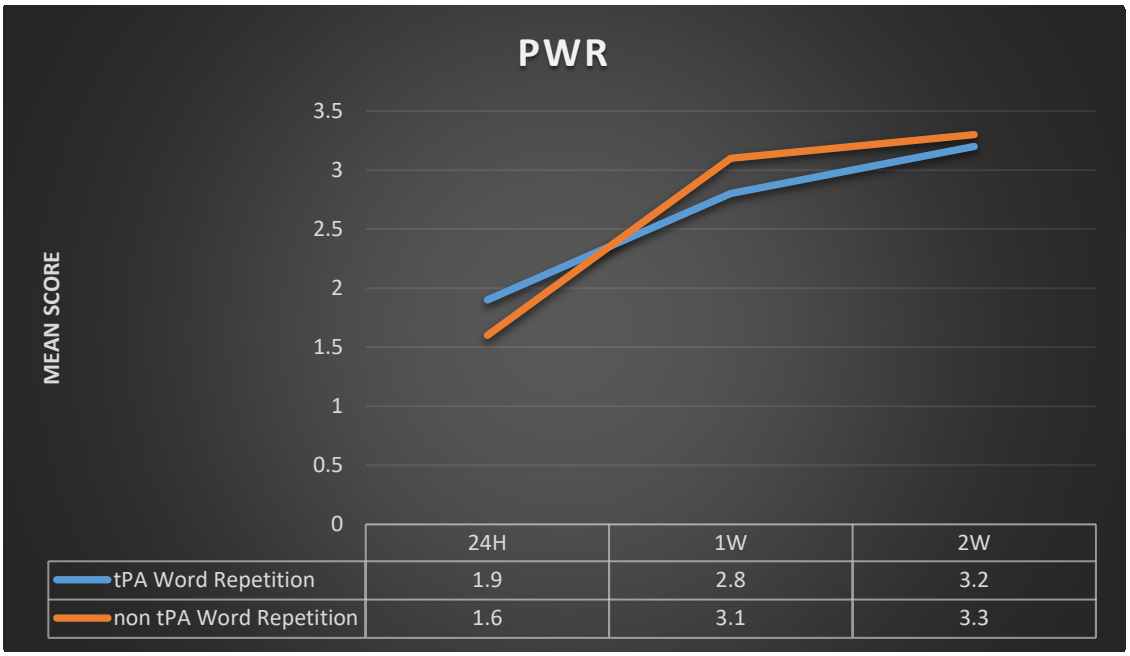


Figure 4.3- % IUs

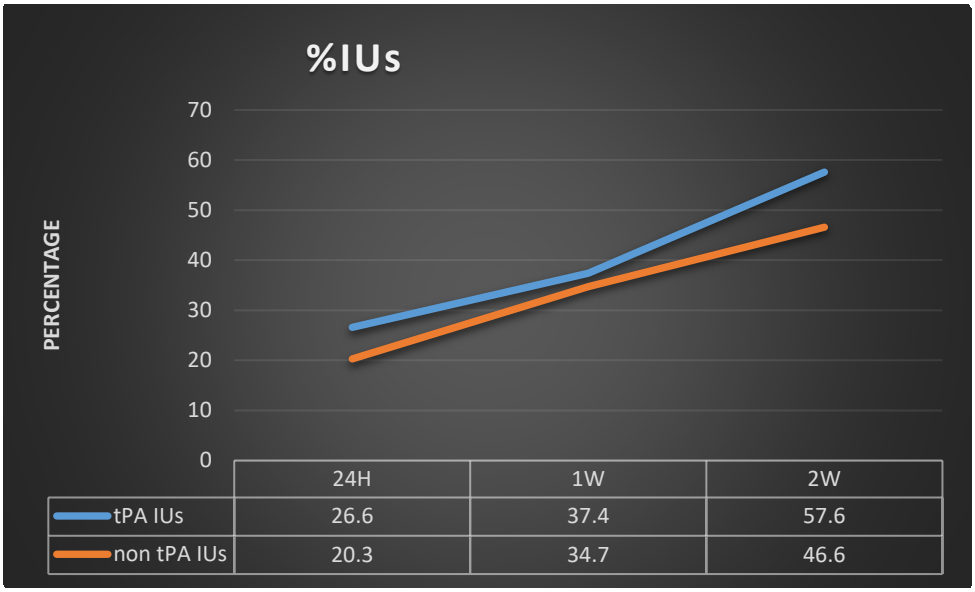


Figure 4.4- WPM

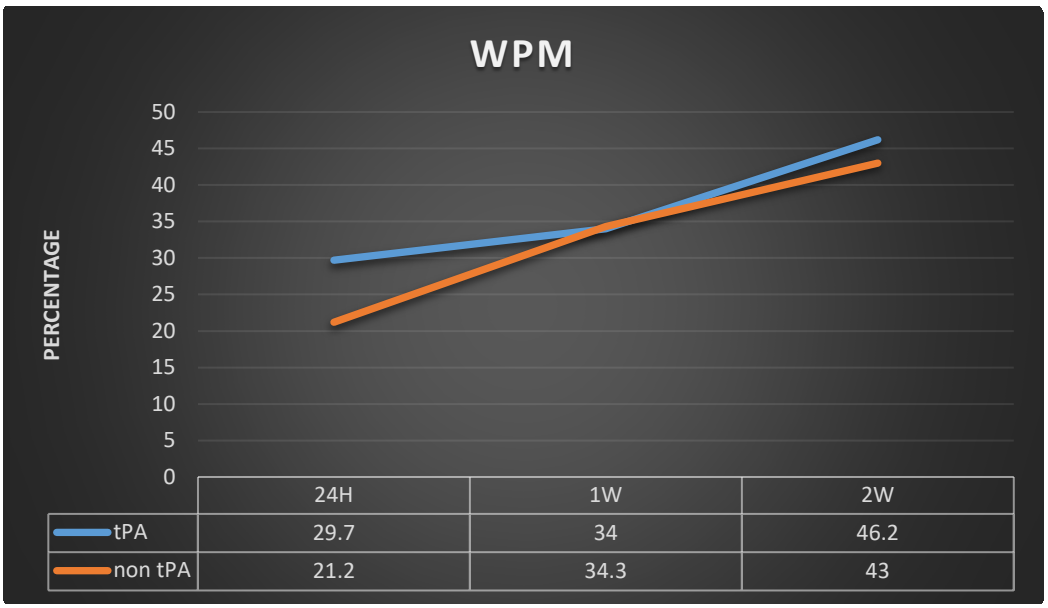


Figure 4.5- PN

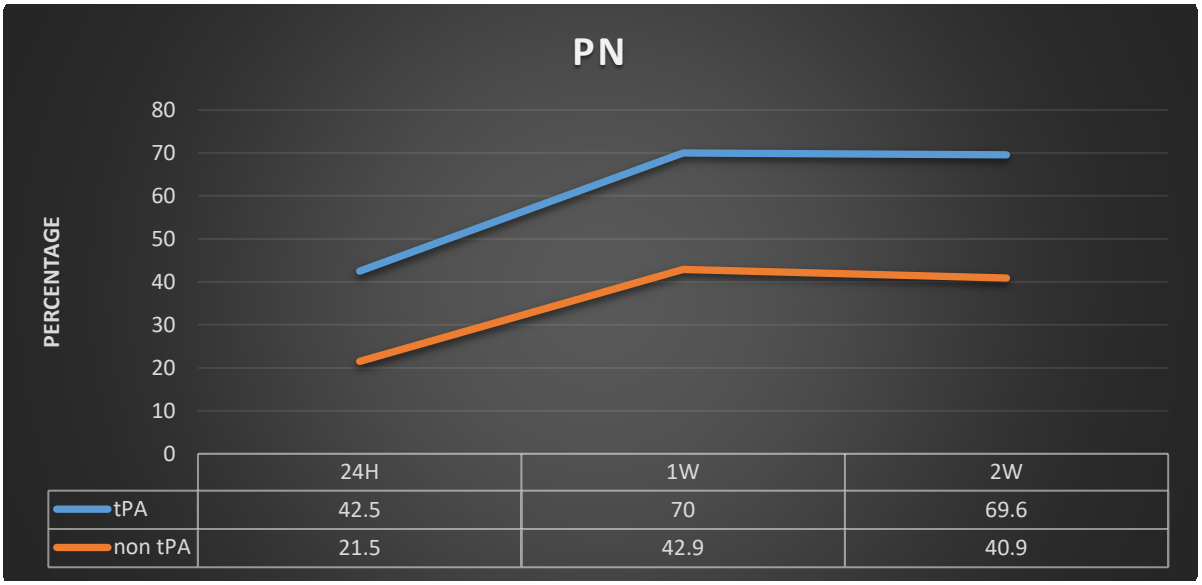


Table 4. 5 Mean change scores and standard deviations from 24 Hours to 2 Weeks for participants who did receive tPA (n=13) and who did not receive tPA (n=13) for Forward Digit Repetition (FDR), Polysyllabic Word Repetition (PWR), Percent Information Units (%IUs), Words Per Minute (WPM), and Picture Naming (PN)

Outcome measure	Group	Mean Change	SD
FDR 24 Hours to 2 Weeks	tPA	26	26.2
	Non-tPA	28	25.3
PWR 24 Hours to 2 Weeks	tPA	1.3	1.4
	Non-tPA	1.3	1.1
% IUs 24 Hours to 2 Weeks	tPA	32.5	31.2
	Non-tPA	24.9	28.2
WPM 24 Hours to 2 Weeks	tPA	17.4	24.1
	Non-tPA	17.1	17.2
PN 24 Hours to 2 Weeks	tPA	27.9	34.1
	Non-tPA	15.5	22.5

Question 3: Do persons with aphasia resulting from a first-ever ischemic stroke who do and do not receive tPA differ on speech, language and quality of life measures at three months post onset, after receiving speech and language therapy?

Eleven of the 26 study participants completed the 3-month assessment. Six of these participants received tPA and five did not. All 11 participants received varying amounts of speech and language therapy between their 2-week and the 3-month assessments in rehabilitation centers, via home health services, or on an outpatient basis. It was not possible to control the type or amount of speech and language therapy given to these participants. The investigator was, however, able to determine the number of hours spent in speech and language therapy by each of these participants. The results of several analyses examining differences in speech and language and quality of life outcomes for these two groups follow.

Table 4.6 shows the mean *change scores* and standard deviations for the tPA (n=6) and non-tPA groups (N=5) for each language task from the 24 hour to the 3 month assessment, and from the 2 week to the 3 month assessments. Table 4.7 shows the mean *scores* and standard deviations for the speech and language tasks for the tPA (n = 6) and non-tPA (n = 5) groups that completed the 3 month assessment. Figures 4.6 and 4.7 also provide illustration of group mean differences for each outcome measure at three months. Mean scores for all five outcome measures were higher in the tPA group compared to the non-tPA group at three months (Table 4.6). However, when considering the mean amount of change on each measure, the tPA group demonstrated a smaller change score compared to the non-tPA group on some tasks (Table 4.7). This may be reflective of the variability of the sample, with some individuals starting at a higher ability level.

To answer Question 3, a MANOVA was utilized first to examine the interaction of a within-subjects factor of time, at 24 Hours, 2 Weeks, and 3 Months, and a between-subjects factor of tPA. Results of this analysis, shown in Table 4.8, revealed that the entire sample improved significantly over time on all five outcome measures. With a between subject factor of tPA, there was a significant difference detected, indicating a significant impact of tPA, on the %IUs, WPM, and PN measures. Post hoc testing was then completed using independent two sample t tests to further investigate group differences on these three measures, with both the mean change scores and mean scores. For the mean change scores from 24 Hours to 3 Months and 2 Weeks to 3 Months, no significant group differences were identified on %IUs, WPM, or PN (Table 4.6). However, when examining the mean scores at three months on these three outcomes, results revealed that scores were significantly higher for the tPA group on each task (Table 4.7). Thus while the mean scores for all the language tasks for the participants that received speech and language therapy between the 2-week and the 3-month assessments were higher for the participants getting tPA (See Table 4.7), the mean amount of change up to 3 months on the various language measures was not significantly different for the two groups (See Table 4.6).

Table 4. 6 Mean change scores, standard deviations, and p values from 24 Hours to 3 Months and 2 Weeks to 3 Months for participants who did receive tPA (n=6) and who did not receive tPA (n=5) for Forward Digit Repetition (FDR), Polysyllabic Word Repetition (PWR), Percent Information Units (%IUs), Words Per Minute (WPM), and Picture Naming (PN)

Outcome measure	Group	Mean Change	SD	*p value*
FDR	tPA	35.8	28.8	NR
24 Hours to 3 Months	Non-tPA	18.6	20.1	
PWR	tPA	2.3	1.7	NR
24 Hours to 3 Months	Non-tPA	2.3	1.6	
% IUs	tPA	42.0	33.9	.86
24 Hours to 3 Months	Non-tPA	39.4	23.3	
WPM	tPA	47.2	25.5	.46
24 Hours to 3 Months	Non-tPA	35.8	23.4	
PN	tPA	60	38.5	.41
24 Hours to 3 Months	Non-tPA	40	38.1	
FDR	tPA	11.3	16.4	NR
2 Weeks to 3 Months	Non-tPA	-2.6	4.1	
PWR	tPA	.67	.75	NR
2 Weeks to 3 Months	Non-tPA	.72	.83	
% IUs	tPA	18.8	19	.41
2 Weeks to 3 Months	Non-tPA	10.8	15.2	
WPM	tPA	21.9	23.1	.74
2 Weeks to 3 Months	Non-tPA	17.2	22.1	
PN	tPA	15	19.7	.82
2 Weeks to 3 Months	Non-tPA	18	23.9	

*alpha 0.10
NR- not reported; based on MANOVA results

Table 4. 7 **Mean scores, standard deviations, and p values for participants who did receive tPA (n=6) and who did not receive tPA (n=5) for Forward Digit Repetition (FDR), Polysyllabic Word Repetition (PWR), Percent Information Units (%IUs), Words Per Minute (WPM), and Picture Naming (PN) for the 3 Month assessment**

Outcome measure	Group	Mean	SD	*p value*
FDR 3 Months	tPA	64.8	30.5	NR
	Non-tPA	48.8	38.2	
PWR 3 Months	tPA	4.7	.49	NR
	Non-tPA	4.0	.67	
% IUs 3 Months	tPA	83	3.4	.01*
	Non-tPA	43.4	30.3	
WPM 3 Months	tPA	93.1	18.9	.01*
	Non-tPA	52.4	21.6	
PN 3 Months	tPA	100	0	.03*
	Non-tPA	52	45.5	

*alpha 0.10
NR- not reported; based on MANOVA results

Table 4. 8 ***p* values for MANOVA on each outcome measure across assessments at 24 Hours, 2 Weeks, and 3 Months for all participants (n=11)**

Measure	Time *p* value	tPA *p* value	Time*tPA *p* value
FDR	.01*	.52	.31
PWR	.02*	.37	.80
%IUs	.01*	.08*	.62
WPM	.01*	.02*	.82
PN	.02*	.04*	.29

*alpha 0.10

Figure 4.6- 3 Month Means: FDR, % IUs, WPM, PN

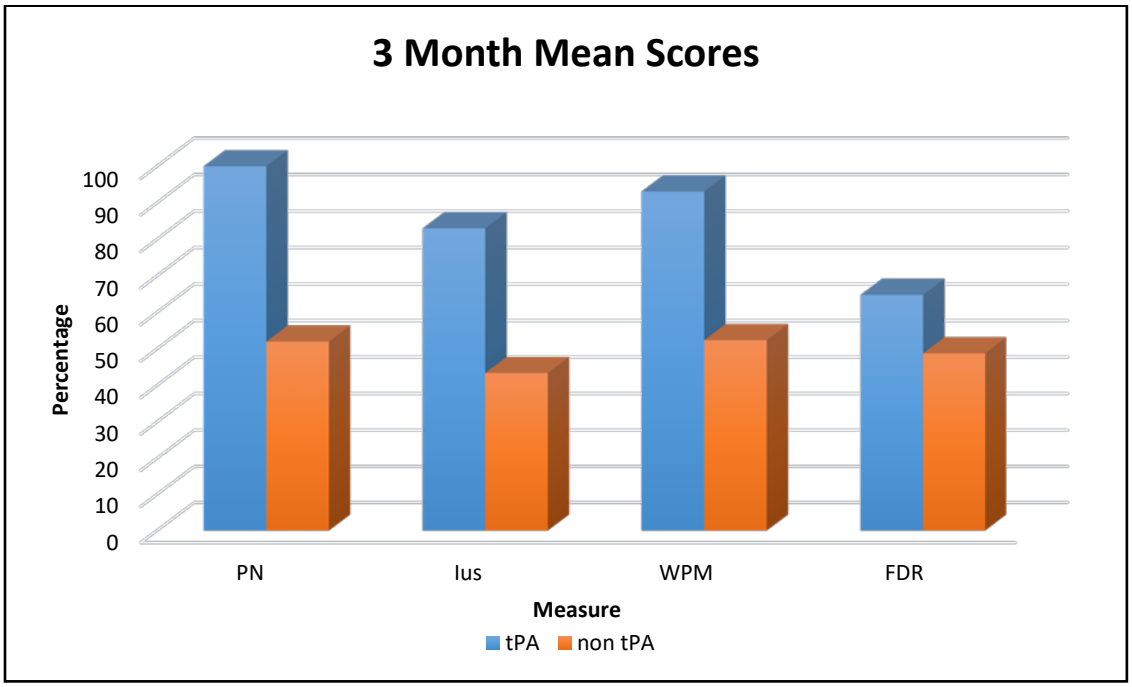
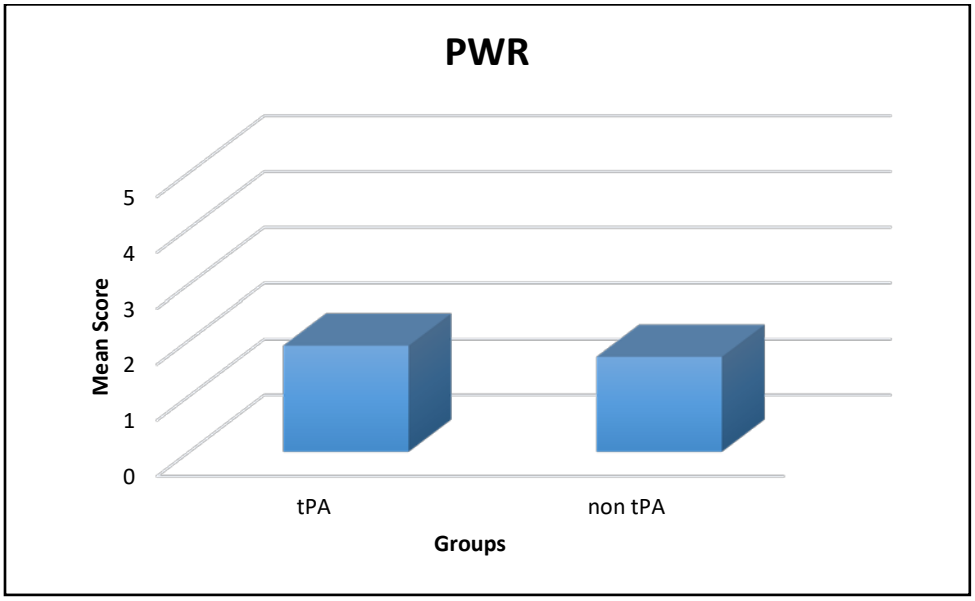


Figure 4.7- 3 Month Means: PWR



The statistical significance detected on certain tasks may reflect upon the sensitivity of those tasks to capture subtle improvements over time. Specifically, information units, word repetition, and confrontational naming may better capture improvement in functional communication after stroke. Of note, because of the small sample of participants that completed this three month assessment, these results are interpreted with caution, simply suggesting evidence that tPA results in better speech and language outcomes at three months, rather than definitive proof.

Although not significant, it is important to highlight that the tPA group in this sample had more severe strokes, as indicated by a higher total NIHSS score [tPA group: 14(6); non-tPA group: 8.8 (8.3); (p=.26)]. However, while the NIHSS total score was higher for the tPA group on admission, the NIH language score was higher at admission for the non-tPA group [tPA group: 2.0 (.63) and non-tPA group: 2.2 (.83); (p=.66)]. This suggests a greater severity of stroke in the tPA group when considering overall impairments; but specific to language, there was a higher level of impairment in the non-tPA group at onset. Also, the tPA group received more total hours of speech therapy [tPA group: 18.6(10.7) and non-tPA group: 6.6 (8.2); (p=.07)] by three months, which was noted to be statistically significant. This is a very important factor to consider in the performance of both groups and is also considered in the regression analysis presented later. The distribution of therapy hours was not specifically tracked but was noted to be variable across participants. While some participants received more intensive therapy earlier within the three month timeframe, the therapy hours for others were more spread out across the three months.

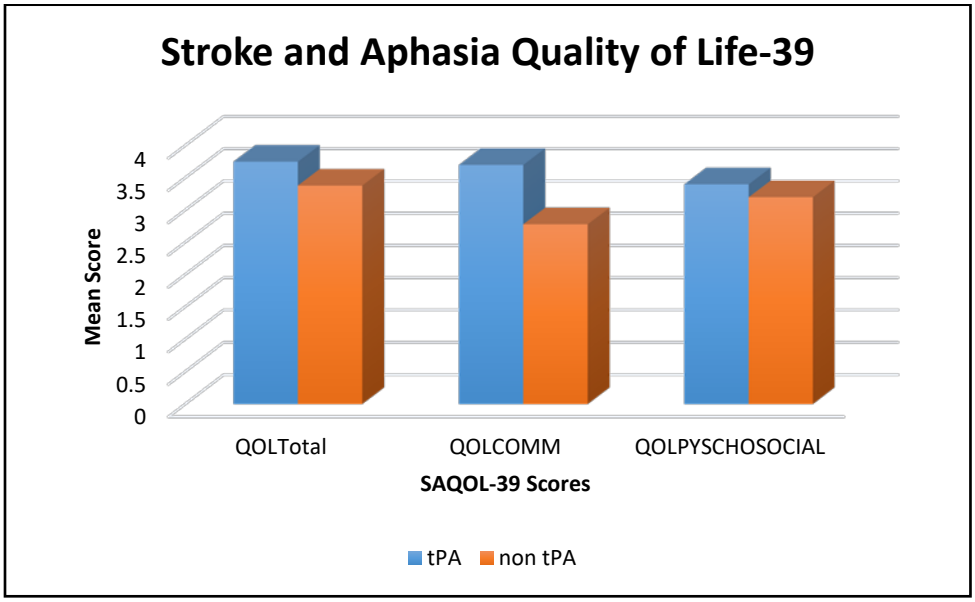
The 11 participants available for the three month assessment completed the Stroke and Aphasia Quality of Life Scale (SAQOL-39), a standardized quality of life measure for individuals with stroke and aphasia. Three scores were calculated for each participant at this time: Total score, Communication domain score, and Psychosocial domain score. Table 4.9 and Figure 4.8 indicate that the Total and Psychosocial scores were very similar for both the tPA and non-tPA groups. As seen in Table 4.9, independent two sample t tests revealed no statistical differences in the scores. Interestingly, the non-tPA group had a slightly higher Total score at 3.9 (.98) versus the tPA group at 3.8 (.82). The difference in Communication score, however, was statistically significant for the tPA group at 3.7 (.82) compared to a 2.8 (.66) for the non-tPA group (p=0.10). Differences between groups suggest higher self-perceived quality of life regarding communication abilities at three months after stroke for those that receive tPA, but not necessarily in regard to overall function.

Table 4. 9 Mean scores, standard deviations, and p values for participants who did receive tPA (n=6) and who did not receive tPA (n=5) for Stroke and Aphasia Quality of Life Scale (SAQOL-39) at 3 Months

Outcome measure (n=11)	Group	Mean	SD	*p value*
SAQOL-39 Total Score	tPA	3.8	.82	.51
	Non-tPA	3.9	.98	
SAQOL-39 Communication Score	tPA	3.7	.82	.10*
	Non-tPA	2.8	.66	
SAQOL-39 Psychosocial Score	tPA	3.4	1.2	.88
	Non-tPA	3.3	1.3	

*alpha 0.10

Figure 4.8: SAQOL-39 Means



Secondary Question

Question 4: In persons with first-ever left hemisphere stroke resulting in speech and language deficits, what other relationships are present between demographic, medical, and therapeutic variables and early speech and language recovery?

The secondary question in the study investigates other possible relationships present among the group between speech and language recovery and quality of life scores and several demographic, medical and therapeutic factors. Multiple regression analyses were conducted to examine the relationship between each outcome measure and various potential predictors. With forward selection, the following were considered in the analysis: age, gender, education, co-morbidity index, polypharmacy, discharge disposition, acute care hospital length of stay, NIHSS total and language scores at admission, and total speech therapy hours at 2 weeks and 3 months. Multiple outcome measures were used in the analysis: 1) the change scores on each measure from 24 hours to two weeks, 2) the change scores on each measure from 24 hours to three months, 3) the two week means and 4) the three month means. The change scores were used to account for the different starting levels with high participant variability. However, the two week and three month means were also used to investigate predictive factors for the end performances at those times.

Regression analysis revealed no significant predictive factors for several of the outcome measures. Age, gender, co-morbidities, polypharmacy, length of stay, and discharge disposition had no linear correlation and were not significantly predictive of performance on speech and language tasks or quality of life. However, as seen in Tables

4.10 and 4.11, results showed that the NIHSS scores, therapy amount at three months, education level, and tPA were all significant predictive factors across various outcome measures.

Two Weeks: No significant predictive variables were identified for the change scores from 24 hours to two weeks. However, as seen in Table 4.10, for the mean scores at 2 weeks (n=26), on the PN task, a combination of the NIHSS Language admission score, tPA, and level of education accounted for 55% of the variance. The beta value indicates the amount that the outcome measure will increase with a one-point increase in the co-variant. The co-variant tPA was coded as 0 (non-tPA) and 1 (tPA), which means that use of tPA increased the PN score by 40.6% accuracy at two weeks. In addition, a one-point increase on the NIHSS language sub score decreased the PN score by 27.6%. At the same assessment point, the NIHSS Language score was also a significant predictive factor for %IUs, accounting for 17% of the variance with a beta value of -21.2, meaning a one-point increase in the NIHSS Language score resulted in a 21.2% decrease in IUs.

Three Months: Table 4.11 shows that when examining change scores from 24 hours to 3 months (n=11), the NIHSS Total admission score, or initial stroke severity, was a significant predictive factor of the amount of change for the PN task (R^2=.450) and FDR task (R^2=.583). The NIHSS Language score was predictive of amount of change on the PWR task at three months (R^2=.366). tPA was a significant predictive factor in the three month mean score of percent information units and words per minute. With percent information units at three months, the tPA explained 53% of the variance within our

sample, with a beta value of 39.6, which means that use of tPA increased the overall PN score by 39.6% at three months.

With WPM, two predictors, tPA and therapy amount at three months, were entered into the regression model. This model explained 78% of the variance, with a beta value in the model for tPA of 58.5. For this measure, the amount of therapy received at three months revealed a small beta and negative value of -1.47, indicating an increase in therapy hours resulted in a decrease in WPM mean score. For therapy amount at three months, no other significant correlations were identified with outcome measures. Finally, for the quality of life outcome measures, the NIHSS Language sub score was a significant predictive factor in the SAQOL-39 Communication domain score, accounting for 45% of the variance, a one-point increase in NIHSS Language score decreasing the Communication domain score by .87 points.

Table 4. 10 Multiple linear regression for all participants (n=26) for 2 week means on Percent Information Units (%IUs) and Picture Naming (PN)

Outcome Measure	Variables	R^2	β
IUs 2 WEEK MEAN	NIHSS Language Admission	.17	-21.2
PN 2 WEEK MEAN	NIHSS Language Admission, tPA, Education	.55	-27.6 (NIHSS) 40.6 (tPA) 11.5 (Education)

Table 4. 11 Multiple linear regression for all participants (n=11) for 3 month means and 3 month change scores for Forward Digit Repetition (FDR), Polysyllabic Word Repetition (PWR), Percent Information Units (%IUs), Words Per Minute (WPM), Picture Naming (PN), and Quality of Life (QoL) measures

Outcome Measure	Variables	R^2	β
IUs 3 MONTH MEAN	tPA	.54	39.6
WPM 3 MONTH MEAN	tPA; Therapy amount at 3 Months	.78	58.5 (tPA) -1.47 (Therapy)
FDR Change from 24H to 3M	NIHSS Total Admission	.58	2.69
PWR Change from 24H to 3M	NIHSS Language Admission	.37	1.37
PN Change from 24H to 3M	NIHSS Total Admission	.45	3.49
QoL Communication Score 3 MONTH MEAN	NIHSS Language Admission	.45	-.87

Chapter 5- Discussion

This study examined early speech and language recovery in individuals with aphasia resulting from a first-ever left-hemisphere ischemic stroke and evaluated the effects of a single neuroprotective treatment, administration of tissue plasminogen activator (tPA) on recovery. From the standpoint of clinical management, this observational study sought to describe changes in speech and language during the acute phase of stroke recovery, so as to provide preliminary information to speech language pathologists about the prognosis and the evolution of patients with aphasia who do and do not receive this neuroprotective intervention.

This study was unique in several respects. First, it constituted the first attempt to carry out a prospective study of the effects of a single neuroprotective treatment (administration of tPA) on a specific symptom (aphasia) associated with ischemic stroke with objective speech and language measures. Most studies investigating the effects of neuroprotective treatments on speech and language have been retrospective in nature or employed the NIH Stroke Scale to estimate stroke severity and severity of patients' language deficits. Secondly, this study was a relatively large group study carried out in a reasonably sized southeastern medical center having a Comprehensive Stroke Program. Many studies examining the impact of neuroprotective treatment on speech and language functions have focused on single cases or small groups of patients. Lastly, this study utilized rigorous selection criteria such as limiting enrollment to individuals with first-ever ischemic strokes. In many respects, the selection criteria employed in the study parallel those of two VA cooperative studies (Wertz et al, 1981; Wertz et al, 1986) that have been constituted as "the gold standard" for aphasia treatment outcome studies for

several years. This proved to be a challenge for completion of data collection but was important to maintain in order to provide the most homogenous sample possible.

This chapter will begin with a discussion of findings and implications pertaining to the primary research questions posited in prior chapters as they relate to (1) speech and language changes in the acute phase of stroke recovery, (2) the impact of tPA on speech and language changes in the acute phase of stroke recovery, and (3) the potential effects of tPA on responsiveness of patients with aphasia to speech and language treatment. This will be followed by a discussion of how certain demographic, medical, and other factors might play a role in determining the impact of neuroprotective treatments such as tPA on speech and language outcomes, challenges of carrying out treatment research in the acute phase of stroke recovery, study limitations, and directions for further research.

Speech and Language Changes in the Acute Phase of Stroke Recovery

Stroke recovery has recently be conceptualized in three phases, acute (onset to 1 month post-onset), subacute (1 month to 3 months post-onset), and chronic (3 months post-onset and beyond), (Kiran, 2012). For many years, stroke survivors with aphasia received speech and language therapy in the acute and subacute phases of recovery, and sometimes into the chronic phase. Since the passing of the Balanced Budget Act (BBA; 1997), however, decreasing acute care length of stays (LOS) and more prompt admission to the rehabilitation hospital have set the stage for most of a patient's aphasia therapy being provided in the acute phase of stroke recovery. This implicates two factors in terms of measurement of early speech and language outcomes, spontaneous recovery and

aphasia treatment. Historically, the term spontaneous recovery has been used to refer to improvements in speech, language and other functions by stroke survivors in the absence of intervention (Brookshire, 2015). These improvements are thought to be the result of reduced edema, restoration of blood flow to damaged areas of the brain, and lessening of diaschesis associated with healing of the brain (Kertesz & McCabe, 1977; Rubens, 1977). Two periods of spontaneous recovery have been recognized, early and late. The former begins as soon as the 2nd or 3rd day post-onset (Rubens, 1977), lasts for approximately two weeks, and is characterized by robust improvements in speech, language, cognitive, and physical functions. The later phase also lasts approximately two weeks and is characterized by more gradual changes in the aforementioned functions (Rubens, 1977; Pashek & Holland, 1988).

Not surprisingly, it is challenging to assess early speech and language changes in stroke patients with aphasia. Most patients with aphasia prefer to begin speech and language therapy in concert with other rehabilitation services as soon as possible after stroke. This complicates early measurement because one cannot determine if the changes are due to the healing powers of spontaneous recovery or the treatment the patient is receiving. Only three studies have assessed early speech and language outcomes for patients with aphasia in the absence of intervention (Culton, 1969; Hartman, 1981; Lendrum & Lincoln, 1985). All of these studies reported no significant changes in speech and language for untreated patients (Rosenbek, LaPointe, & Wertz, 1989) after approximately two months post-onset. Additionally, these studies completed their first measure nearer the end of the first month post onset whereas the present study assessed changes much sooner after stroke onset.

The findings of the present study provide new information regarding the timeframe for and degree of speech and language improvement in untreated aphasic patients in the acute phase of stroke recovery or what is also referred to as early spontaneous recovery. First, findings of this study indicate speech and language improvement in first-ever ischemic stroke patients with aphasia are discernable as early as 1 week post-onset (See Table 4.1). When changes on the FDR, PWR, %IU, WPM, and PN were examined for the 26 participants, irrespective of tPA status, significant improvements were noted for all five tasks from the 24 hour to the 1-week and 2-week assessments respectively. While some of these patients received support, guidance, and a bedside evaluation from speech-language pathologists while in the acute care or rehabilitation hospital, study participants were essentially untreated during the first week. Thus, this study provides information regarding early changes in speech and language for untreated stroke patients with aphasia at a much earlier point than in prior studies. Significant improvement from the 1-week to the 2-week assessment was evinced for two of the five tasks. Participants received varying amounts of speech and language therapy during this timeframe, ranging from 0-6 total hours. While the sample was not completely untreated, it was not possible or ethical to totally prevent participants from getting any services of a therapeutic nature. Importantly, the significant improvements during this timeframe were on the measures associated with describing a picture, %IU and WPM, and changes in the modality deemed most important by patients and clinicians, talking. Improvements in speaking so early in the post-stroke course and at a time when many patients are still in the hospital suggest that speech-language pathologists in acute care settings should promote the use of conversation early as

suggested in many clinical papers directed at improving services to patients in the acute phase of stroke recovery (Beyn & Shokhor-Trotskaya, 1966; Holland and Fridriksson, 2001; Marshall, 1997; Murray & Holland, 1995). While the frequency of acute care aphasia treatment sessions has decreased with healthcare reform, and are currently reported at an average of 1-3 sessions per week (Bernhardt, Chan, Nicola, & Collier, 2007; Kong, 2011; McKenzie et al, 1993; Verna, Davidson, and Rose, 2009), the acute care speech-language pathologist should spend his or her limited time in supporting conversation and functional communication. This would also include providing education to the healthcare team on supporting language improvement through conversation during the acute care stay. Finally, findings of this study provide added support to the premise that speech and language improvements associated with spontaneous recovery in untreated patients are more or less confined to the first week post-onset and may dissipate earlier than has been previously thought. A much larger study by Pederson and associates provides some support (Pederson, Jorgenson, Nakayama, Raaschou, & Olson, 1995). These researchers, in a study of 330 patients with aphasia, found that 84% of the participants studied reached maximum improvement on a standardized Swedish language test at two weeks post-onset. Notably however, the Pederson study examined outcomes for both treated and untreated aphasic patients.

Researchers have judiciously avoided investigating the impact of speech and language therapy in this early timeframe because of the impact and variability of spontaneous neurological changes. However, health care practices and reduced hospital length of stays now make it necessary to provide most of the treatment for an individual with aphasia in the acute phase of stroke recovery. This dictates the need to investigate

the combined influences of spontaneous recovery and the impact of early speech and language therapy. Results of the current study support the need for this.

Determining the Impact of Neuroprotective Treatments in the Acute Phase of Stroke Recovery

Neuroprotective treatments have been shown to minimize the disabling consequences of stroke (NINDS, 1995; Hacke et al, 1995; Hacke et al, 1998; Hacke et al, 2008; Clark et al, 2000; Clark et al, 1999; Goyal et al, 2015; Berkhemer, 2015; Saver et al, 2015). Nevertheless, these treatments are costly and involve risks, and empirical studies are needed to prove that neuroprotective treatments are efficacious in minimizing or preventing disability associated with residuals of a stroke beyond what might result without the treatment. The present study examined outcomes for a single neuroprotective treatment, tPA, on early speech and language outcomes for patients with aphasia, a symptom associated with left-hemisphere stroke. This study had a total of 26 study participants; 13 were administered tPA based on a neurologist's decision, and 13 were not administered tPA. Two sample t-tests (See Table 4.2) were used to examine differences between the two groups for selected demographic (age, gender, level of education, Charlson Comorbidity Index, polypharmacy rating, NIHSS overall and language scale scores) and no group differences were found.

Selected speech and language skills of participants who did and did not receive tPA were assessed three times in the first two weeks post onset, at 24 hours, 1-week, and 2-weeks post-onset. Performance on five tasks, FDR, PWR, %IU, WPM, and PN tasks

was examined in two ways, between-group comparisons on each task (See Table 4.4) and mean change scores for the group on each task (See Table 4.5) with a series of separate statistical analyses. MANOVA results examining factors of time, tPA administration, and the interaction between these variables did not reveal any significant differences (See Table 4.3) on the PWR, %IUs, WPM, and PN tasks, precluding the need to conduct any post hoc comparisons. Table 4.3 reveals that the time factor was significant for all tasks. The tPA factor was not significant for any task and the time by tPA interaction was significant only for the FDR task. Post hoc testing for FDR revealed no group differences on this task at any assessment.

Essentially, when examining the data, between group comparisons for mean scores and change scores for tPA and non-tPA groups duplicate those for the study sample as a whole (See Table 4.1). That is, participants improved across the three assessment points, 24 hours, 1 week, and 2 weeks on all measures. Figures 4.1, 4.,2, 4.3, 4.4, and 4.5 provide a visual representations of the performance of the tPA (blue) and non-tPA (red) groups for the FDR, PWR, %IU, WPM, and PN tasks for the 24 hour, 1 week, and 2 week assessments respectively. Here it can be seen that the difference in performance over time between the two groups is minimally discernible. In fact, at some assessment points, the non-tPA group had a higher mean score than the tPA group on the FDR, PWR, and WPM measures. One notable exception is the PN task. Although performance in picture naming of items from the Philadelphia Naming Test did not differ significantly between the tPA and non-tPA groups, the scores for this task as shown in Figure 4.5 appear to be strikingly different and much higher for the tPA group.

Findings of this study suggest that it may not be possible to detect the effects of a neuroprotective treatment such as tPA on the speech and language outcomes of stroke patients with aphasia in the first two weeks post-onset. While other studies have revealed a significant impact of tPA on speech and language recovery, as evidenced by changes in the NIHSS scores, within the first two weeks (Denier et al, 2015; Kremer et al, 2013), the current study does not corroborate those findings with use of objective speech and language assessments. There are a number of possible explanations for this. One noteworthy explanation is the variability in performance on all of the speech and language measures for individuals in the tPA and non-tPA groups. This is clearly evident in the large standard deviations for all mean scores (See Tables 4.2, 4.4, and 4.5). Lesion size and site may also contribute to the variability but were not analyzed in this study and it would be informative to try to account for the influence of this factor in future studies. The fact that verbal tasks were selected as outcome measures may also have contributed to this variability, since the demand to produce verbal output for these individuals may be too difficult during this timeframe.

The speech and language tasks were chosen because they are routinely used by SLPs to assess persons with aphasia at the bedside in the acute care hospital and spoken language expression is of the utmost importance to stroke survivors with aphasia. However, these tasks may be ill-suited for use with acute stroke patients with aphasia in the acute phase of stroke recovery, particularly when so many patients manifest co-occurring motor speech deficit, not controlled for in this study. Perhaps, as measures such as eye tracking, auditory evoked potentials, and other indices that preclude making a verbal response, are adapted for use in clinical environments, these might be better tools

to assess the effects of neuroprotective treatments such as tPA in the time frame when the patient's ability to respond verbally is limited.

Variability of performance on the language tasks across all four assessments for all participants may also be attributed to the challenges of being in the acute care hospital. In the early post-onset period, hospitalized stroke patients frequently suffer bouts of fatigue as they are assailed with demands associated with medical care, laboratory tests, imaging and trying to recover from a near-death experience. Ideally, it would have been advantageous to assess all participants at the same time of day and control for a fatigue factor. This was, however, impossible to do and patients were assessed at times of the day convenient to the schedule of the investigator and when participants were available.

While the verbal tasks used in the study were sensitive to changes over time for all patients, they were not sensitive enough to discern differences in patients who received tPA. This calls into question the reliance on the language subscale of the NIHSS of 0 = none; 1 = mild; 2 = moderate-severe, and 3 = global as an indicator of aphasia recovery. Many previous tPA studies claim significant improvement in speech and language in patients with aphasia, even within one week of stroke onset, based on use of the NIHSS language score (Denier et al, 2015; Kremer et al, 2013; Lundstrom et al, 2015; Maas et al, 2012; Martins et al, 2017; Menier et al, 2010). While the overall scale does provide crucial ongoing assessment as a measure of global severity of stroke throughout the acute care stay, it provides only broad assessment of changes in aphasia. Moreover, while the NIHSS is considered the gold standard by medical professionals to document neurological improvements or declines over time, it does not offer detailed information about speech and language skills. Therefore, improvements identified by the NIHSS in

earlier studies may not provide the objective data to depict a patient's ability to communicate and should be interpreted with some caution.

In sum, while no differences in speech and language outcomes between patients receiving and not receiving tPA were found, this should not be interpreted to mean tPA does not impact speech and language outcomes for patients presenting with aphasia following a first-ever ischemic stroke. Rather it may indicate a need to further refine our measurement techniques and/or measure at different time.

Impact of tPA on Speech and Language Therapy Outcomes and Quality of Life

Eleven participants completed the 3-month assessment. This assessment involved re-administration of the FDR, PWR, %IU, WPM, and PN tasks and completion of the Stroke and Aphasia Quality of Life Scale (SAQOL-39). The investigator's intention was for all 26 participants to complete the 3-month evaluation, but three participants died, and 12 were lost to follow up after the 2-week assessment. Of the 11 participants available for the 3-month evaluation, six received tPA and five did not. All 11 participants received speech and language therapy between the 2-week and the 3-month evaluation in varying amounts. Differences in the groups on the various speech and language outcome measures and the SAQOL-39 scale were examined to ascertain the potential impact of tPA on treatment outcomes.

tPA and Therapeutic Outcomes

To investigate the impact of tPA on the 3-month outcomes of the tPA group (n=6) and non-tPA group (n=5), a MANOVA was first used to examine a within-subjects factor of time (24 hours, 2 weeks, and 3 months), a between-subjects factor of tPA, and the interaction of these two factors. As presented in chapter 4, results of this analysis revealed that the sample of 11 participants improved over time on all five outcome measures and the between-subject factor of tPA was significant for % IUs, WPM, and PN. When group mean scores were compared on these three speech and language outcome measures at 3 months post-onset and after the participants had finished their speech and language therapy course, the tPA group evinced significantly higher scores on the same three outcome measures as shown in Table 4.7. These results suggest that tPA may positively impact responsiveness of patients with aphasia to speech and language therapy, but they warrant cautious interpretation because of the small sizes of the groups and the differences in amount of therapy received by each group. Results also indicate that it might be advantageous to assess the effects of neuroprotective treatments such as tPA later rather than sooner as there were relatively few differences between subjects getting and not getting tPA until the 3 months evaluation. Strategies for accomplishing this and a rationale for examining the effects of neuroprotective treatment in the long rather that the short term will be presented in a subsequent segment of the discussion on research implications.

Quality of Life

Differences in self-perceived quality of life on the total and psychosocial scores of the SAQOL-39 between the tPA and Non-tPA groups after therapy were not significant, but nearly identical, as seen in Figure 4.8. However, the mean communication score on the SAQOL-39 was significantly higher for the participants that had tPA. The disparity in the mean communication score on the SAQOL-39 for the groups may reflect the fact that the tPA group had received significantly more hours (p =.07) of speech and language therapy (Mean =18.6 hours; SD=10.7 hours) than the non-tPA group (Mean = 6.6 hours; SD = 8.2 hours) at 3 months post-onset. Since participants in both groups were aphasic and severity of aphasia did not differ for the groups as determined by language scores on the NIHSS at the time of hospital admission, it raises the question of why the tPA group received significantly more therapy. Although speculative at this time, the differences in the speech and language treatment hours for the groups and the possible impact of these hours on the communication score for the SAQOL-39 may reflect the amount of time spent in the rehabilitation hospital by members of each group. Examination of the total NIHSS scores for the participants completing the SAQOL-39 scale after speech and language therapy revealed that the mean total score for the tPA group on the NIHSS (Mean = 14; SD = 6) suggests that they had incurred more severe strokes than the non-tPA group (Mean = 8.8; SD = 8.3). This may have caused them to spend a longer amount of time in the rehabilitation hospital and to have logically received more therapy. Subsequently, the extended time in speech and language therapy may have positively influenced their self-perception of communication skills.

Regression Analysis

In the regression analysis completed in this study, various factors and their impact on outcome measures were included for consideration. The only significant factors that emerged were tPA, stroke severity, level of education, and total therapy hours at three months. In contrast to previous studies (Chapey, 2008; Goldstein, 1995; Goldstein, 1998; Holland et al, 1989; Ogrezeanu et al, 1994; Sarno et al, 1992), age, gender, comorbidities, and medications were not identified as significant factors in recovery.

An important result central to the aim of this study was the fact that tPA was significant to predict performance on picture naming and discourse tasks at varying assessment points. Of note, tPA generally had large beta values, indicating that the use of tPA resulted in large increases in outcome scores. This is particularly true with the PN task means at 2 weeks and the discourse tasks at 3 months, supporting the theory that these verbal output tasks appeared to be most sensitive to change after tPA. In fact, the beta value for tPA as a predictive factor of the mean %IU at 3 months was nearly 40. An increase of 40% more relevant, informative content in a language sample can make a substantial difference in the functional communication and independence of an individual with aphasia. This provides additional support for the later effects of tPA with regard to speech and language recovery.

Another significant factor in recovery in this study was initial stroke severity and initial aphasia severity, represented as two separate scores by the NIHSS upon admission to the acute care hospital. It is well-established (Inatomi et al, 2008; Kertesz & McCabe, 1977; Lazar et al, 2010; Hojo et al, 1985; Plowman et al, 2011) that the severity of

aphasia at onset significantly correlates with both early and long-term improvement of aphasia and this study continues to validate that finding.

As mentioned earlier, the differences in speech, language, and quality of life outcomes between groups at three months should be interpreted with caution because of both the small sample size and the fact that the tPA group received significantly more hours of speech and language therapy. Further analyzing this as a potential variable, the total amount of hours in therapy was included as a predictive factor in the regression analysis. Interestingly, this variable was only a significant predictor of the mean WPM score at 3 months and actually had a negative predictive value, with a small beta of -1.47. This indicates that an increase in therapy hours resulted in a decrease in WPM mean score, which is in direct contrast to the expected impact. For therapy amount at three months, no other significant correlations were identified with outcome measures, suggesting that the impact of speech and language therapy on these 3-month outcomes warrant further consideration and analysis.

Limitations

The number of early treatment outcome studies involving individuals with aphasia is minimal due to some very real hurdles. Logistical challenges and limitations are highlighted by the current study, substantiating the lack of evidence in this area.

First, the small sample size in this study may have impacted the results, especially considering the large amount of variability within the sample. An a priori sample size analysis was completed and I was able to recruit the calculated 13 per group for 80%

power, so we can be confident in significance testing completed for the study. However, increasing the sample size would have increased the homogeneity of each group, providing a more representative sample of the population to study. The small sample size at the 3-month follow up is a further limitation. The results suggest evidence that by this assessment, tPA has significantly improved the speech and language skills of those that received it. However, due to the small groups, it is impossible to state this fact confidently. Considering the findings, a larger study would certainly be justified and warranted.

The sample size in this study was highly impacted by challenges with recruitment. The inclusion criteria were a major impediment to recruitment. Of more than 600 patients screened over 2.5 years, only 32 met inclusion criteria. Over 30% (214) had suffered a prior stroke, excluding them from this study. It is very common for a person admitted with stroke to have a previous history of stroke but this inclusion criterion was very important to maintain in order to rule out any residual effects of the prior infarct, potentially confounding the results. The recruitment challenges in this study are consistent with previous studies limited by rigorous inclusion criteria. For example, Nesi et al (2012) screened 2350 potential participants over the course of seven years, with only 128 meeting criteria to participate. Similarly, Denier et al (2015) needed five years to enroll 137 individuals with aphasia who received tPA, supporting that this particular challenge is common.

In general, recruitment and conduct of early outcomes research can also be compromised due to other factors, such as the shortened length of stay for patients with stroke. Due to reimbursement changes, the person with a stroke is discharged from the

acute care hospital much more quickly than in the past. This can make studies with follow-up more challenging and difficult to complete, with a higher risk of attrition. Also, in this early window after stroke, prospective subjects can be difficult to approach early due to the gravity of the current situation, the myriad of procedures they are completing, or even simply fatigue. Some of these factors were present in the current study, specifically increasing the burden upon the investigator to complete assessments within the necessary timeframes.

Another limitation is the fact that this study included participants admitted with a diagnosis of stroke to a single hospital. This limited the application of the results to a single facility within a single geographical location, which may possibly introduce bias and limit generalizability of the results. For this reason, the study should be considered as exploratory and a first step in objectively evaluating early speech and language recovery.

Additional threats to internal validity include selection bias, repeated testing, and experimenter bias. Convenience sampling was used based on admissions to the medical center and was at times confined within the schedules of the investigator and research assistant. This may have inadvertently introduced some bias into the results. A testing effect may be present in the data as well since subjects received multiple assessments within a 2-week window of time. While the speech and language stimuli were presented in alternating fashion as much as possible, some of the tasks were presented in the same format at each assessment. As a result, familiarity with the testing stimuli could potentially introduce additional bias. Experimenter bias is also present as the primary investigator was the one collecting all data and scoring a portion of it. This was unavoidable, however, based on the design of the study and frequency of assessments.

A final limitation includes the study's inability to gather a true baseline assessment. The first assessment done with this sample was within 24 hours of stroke onset. Ideally, however, the first assessment would have occurred after stroke onset but before initiation of tPA. Considering the hospital's prompt response time and process for medical diagnosis, an assessment by the speech pathologist just is not feasible that quickly (Maas et al, 2012). Moreover, previous studies (Kremer et al, 2013; NINDS, 1995) have revealed insignificant changes within 24 hours of onset, particularly when comparing those who get tPA and those who do not, further justifying the decision to design the study with the first assessment after tPA but within 24 hours of stroke onset.

Future Research Implications

Next steps in research following this current study would include expansion of the current investigation as well as replication with other outcome measures and other patient populations. First, I would like to continue to recruit and gather data on the current study. Increasing the sample size, as stated above, would only help to validate results and potentially reduce the variability and standard deviations within the sample data. If I could add more participants and complete the 3-month follow up, I may be able to more confidently report the significance in differences between the tPA and non-tPA groups at that assessment. Additional participants would help to further illustrate how these individuals are changing during the first two weeks and three months after their stroke. This could also include expansion in pursuing additional sites, in order to reduce some of the bias as discussed.

In addition to increasing the sample size by continued recruitment, further analysis of already collected data would add to the initial interpretation. Some data were collected but, in order to keep the product of this study focused, were not included in statistical testing. For example, I would like to continue to review and analyze the amount of speech and language therapy received at 3 months by our participants. Although regression analysis did not reveal any positive relationship, a more detailed and individualized review of each participant may inform further statistical testing. Likewise, investigating the LOS in acute care and rehabilitation/extended care facilities, as well as differences between these discharge dispositions, could potentially provide more information about the impact of a comprehensive rehabilitation program on speech, language, and quality of life outcomes. Additionally, it would be important to consider the physical impairments for participants and the influence those may have on our results. Physical limitations negatively impact overall quality of life post stroke (Charfi et al, 2017; De Wit et al, 2017; Ellis, Grubaugh, & Egede, 2013; Krzeminska, Bekus, Borodzicz, & Arendarczyk, 2016) and improvement of physical health significantly improves quality of life (Gordon, Wilks, & McCaw-Binns, 2013). The quality of life survey results in this study support the theory that physical impairments may be more important to perceived quality of life than communication. Although the physical domain SAQOL-39 scores were not included in analysis, this would be an important next step to investigate its potential impact on quality of life in the included sample.

Next, I believe it would be important to replicate this study with other outcome measures. While the current study focused solely on speech and language tasks that primarily assessed verbal expression, the same procedure could be completed with tasks

focused on auditory comprehension, written expression, and written comprehension. These four main modalities are often impacted by aphasia in varying degrees. The relationship of changes in one versus another after tPA may be of interest and have important clinical application.

Since the current study highlights the potential later effects of tPA on speech and language, it would also be important to complete a study with more longitudinal data. The timeframe of recovery in this study seems to align with previous studies finding that speech and language skills are later to respond to the tPA intervention. While studying dramatic recovery of individuals post tPA at the end of infusion, Felberg and colleagues (2002) observed a pattern of recovery with individual impairments. Gaze deviation recovery, sensory recovery, and motor leg movement were among the first to emerge while aphasia and dysarthria were the last impairments to recover. Mukilik et al (2010) discovered a similar pattern with aphasia only partially responding to the tPA by the end of infusion while many other impairments resolved completely. Data from the current study support the theory that aphasia may have a later response time to tPA. The three month follow up as a stopping point, although consistent with other studies (Jacquin et al, 2014; Kremer et al, 2013; Lundstrom et al, 2015) was a limitation of this study, given the fact that significant differences did not emerge in the groups until sometime between two weeks and three months. In fact, based on the current results, a compelling study would be one in which the participants are recruited in the acute care hospital and intentionally matched on various factors. In contrast to the current study, the assessments would start after acute care discharge, with bimonthly or monthly assessments that continue until twelve months after stroke. This would provide an ongoing long-term investigation of

differences in groups after tPA, avoiding the early spontaneous recovery phase. I believe a study like this would provide very important evidence that could help clinicians in maximizing rehabilitation time and understanding expected prognosis.

The current study focused solely on individuals who received intravenous tPA. However, use of endovascular treatment, or mechanical thrombectomy, as a neuro-protective intervention is rapidly becoming the gold standard for treatment. The mechanical thrombectomy procedure is completed in the presence of an occlusion in a large blood vessel, or ELVO (Emergent Large Vessel Occlusion), and involves removal of the clot. It is commonly completed concurrently with administration of tPA but can be completed within a much larger timeframe, up to eight hours post onset. At the hospital where this study was completed, the rates of mechanical thrombectomy have increased exponentially since we began recruitment. Since the procedure was completed infrequently at the onset of the study, individuals who had this procedure were not included in the sample.

Overall, use of mechanical thrombectomy has been found to be a superior treatment compared to tPA alone, with improved neurological outcomes based on the mRS (Goyal et al, 2015; Berkhemer et al, 2015; Saver et al, 2015) and functional independence scores, returning home more quickly (Campbell et al, 2015). Given the overwhelming evidence that endovascular treatment results in much different outcomes compared to tPA, future research in early speech and language recovery should include participants that receive thrombectomy. Gaining knowledge of the impact of these early neuroprotective interventions on early speech and language changes would be invaluable to acute care speech language pathologists.

Finally, the current study did not investigate the impact of any psychosocial factors on early recovery of stroke. Basic demographic and medical variables were analyzed. However, the impact of social support was not considered in that analysis. When assessing overall functional status, strong social support after stroke results in decreased functional limitations (Colantonio, Kasl, Ostfeld, Berkman, 1993; Glass, Matchar, Belyea, & Fuessner, 1993), improved community participation (Beckley, 2007), and increased quality of life (Hilari & Northcott, 2006). The quantity and quality of the social network and its impact on early speech and language recovery after stroke has yet to be studied. Likewise, the relationship of the social network to the impact of tPA would be interesting to evaluate, adding more to the body of literature related to aphasia prognosis and early management by the speech language pathologist.

Conclusion

This novel study was the first prospective investigation to evaluate the early speech and language outcomes of individuals who do and do not receive tPA in an objective, systematic method. Although some limitations are recognized, results validate early recovery of skills within the first two weeks, regardless of receipt of tPA and in the absence of any speech and language therapy. Differences between those who got tPA and those who did not were not significant until after the two week assessment. By three months, it appears that individuals who did receive tPA have significantly improved outcomes and higher self-perceived quality of life related to communication abilities. Helping inform speech language pathologists in this early timeframe, the results add to the small body of literature focused on the acute phase of aphasia recovery.

Appendices

Appendix A- CID Everyday Speech Sentences (Dais and Silverman, 1978)

Instructions: The researcher will read the following sentences aloud to participants. Participants will repeat sentences verbatim.

Passing Criterion: 9/10 correct

ITEM	Correct	Incorrect
1. It's time to go.		
2. If you don't want these old magazines, throw them out.		
3. Do you want to wash up?		
4. It's a real dark night so watch your driving.		
5. I'll carry the package for you.		
6. Did you forget to shut off the water?		
7. Fishing in a mountain stream is my idea of a good time.		
8. Fathers spend more time with their children than they used to.		
9. Be careful not to break your glasses.		
10. I'm sorry.		
TOTAL		

Appendix B- Vision Screening

VISION SCREEN

Name: _____ Date: ___

Circle the word *good* each time you see it. Read left to right.

good

breath	good	take	moth	home	good
bye	one	good	good	bee	shine
good	good	baby	house	shirt	good
see	nose	good	good	hope	fine
good	show	tired	pies	seem	good

good	table	shine	carpet	good	good	team
paste	good	glue	time	girl	gone	good
good	born	shout	socks	pick	tone	glow
glow	good	point	there	see	good	pass

good	table	shine	carpet	good	good	team
paste	good	glue	time	girl	gone	good
good	bom	shout	socks	pick	tone	glow
glow	good	point	there	see	good	pass

Fig. 16.9. Word scanning/cancellation task for vision screening. (From *Augmentative and Alternative Communication.* Copyright © 1998 by David Beukelman & Pat Mirenda.)

Appendix C: Forward Digit Repetition

Instructions:

- Participant was informed that he or she would be read a list of numbers aloud by the examiner and that he or she was to repeat the numbers as best as possible

Number Lists Used

5-digit	*6-digit*	*7-digit*
4-7-2-9-8	7-0-6-3-5-1	2-3-0-5-4-8-2
3-7-0-9-1	4-6-2-8-9-3	9-6-7-3-2-7-5
5-2-2-6-8	6-5-8-2-1-4	5-3-6-8-6-3-0
9-6-7-3-5	2-2-4-7-9-5	2-1-8-0-8-7-6
1-6-3-8-0	5-0-7-3-1-3	4-6-7-7-1-9-3

Data Collection

- All digit sets presented verbally
- Stimulus and response both audio-recorded
- No prompting or repetition provided
- Termination criteria: Error on five consecutive sets

Scoring Procedures

- Scorer blinded to participant and assessment point
- Participant was given credit for any digit in the string repeated in the correct location of the series. For example, if asked to repeat "2-5-8-4-7," the response was "4-5-4-4-7," the subject was credited for repeating three of the five members of the digit string correctly (see underlined items).
- Because not all participants were able to repeat six or seven digit strings, a post-hoc decision was made to score this task for accuracy for the five digit strings only. In the final analysis, FDR scores represented the number of digits repeated correctly for the five sets of five-digit stimuli. This provided a percentage of accuracy for X/25.

Appendix D: Polysyllabic Word Repetition

Instructions:

- Participant was instructed that the examiner would say some words one-at-a-time and he or she was to repeat the word after the examiner as best as possible.

Word List Used

1. Animal
2. Snowman
3. Artillery
4. Stethoscope
5. Rhinoceros
6. Volcano
7. Harmonica
8. Specify
9. Statistics
10. Aluminum

Data Collection

- Each word presented verbally for immediate repetition
- Only the participant responses were audio-recorded
- The same ten words were presented for each assessment, but in a different order
- Termination criteria: The task was terminated if the participant failed to respond or indicated that he or she could not respond to five consecutive words

Scoring Procedures

- Responses were scored using a 0-5 point scale from the Everyday Speech Production Assessment Measure (E-SPAM; Watts, Marshall, Olson, & Kleinert, 2014), shown below
- To calculate the participant's score for this task, ratings were summed and averaged. Items not responded to were scored as "no response"

E-SPAM Scoring Scale

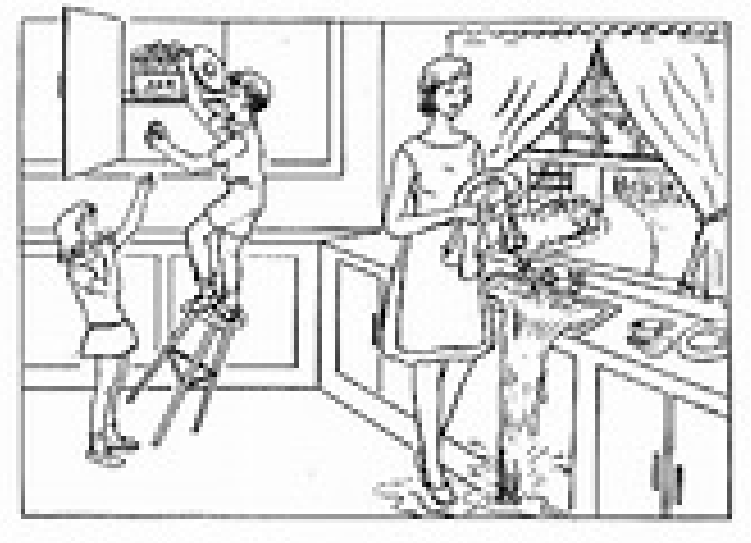
Score	Description	Details
0	**No Response**	The patient is unable to produce a verbal response, informs the examiner he/she cannot respond, or refuses to respond.
1	**Unrecognizable**	The patient produces a verbal response, but the response is not recognizable and offers the listener little-to-no basis for making a guess.
2	**Marginal**	The final response is produced with considerable effort and/or after much struggle and is only recognizable because the listener knows the target utterance; the listener would be able to select the target utterance from a list of choices.
3	**Approximated**	The final response is recognizable as the target response, but is altered prosodically, distorted, stiffly produced, or occurs after an effortful period of self-correction. Although the utterance is recognizable, it would always be perceived as abnormal by a listener.
4	**Corrected/Restarted**	The initial response is partially or completely incorrect, but the final response is normal in every aspect except for the fact that it occurred after a self-correction or re-start.
5	**Normal**	Normal response

Appendix E: Picture Description

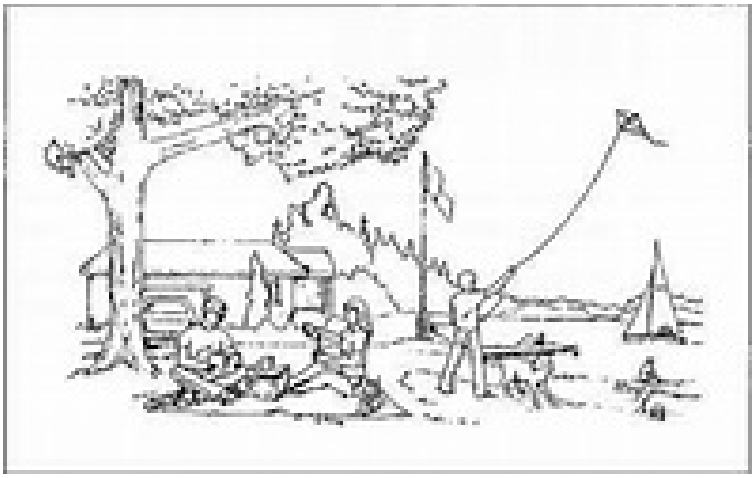
Instructions: "I would like you to look at this picture and tell me about it. Try to use sentences and tell me what you see happening."

Pictures Used

COOKIE THEFT PICTURE



PICNIC SCENE



Data Collection

- Narratives were audio recorded
- Participants were given up to 1 minute to respond with each picture
- Both pictures were attempted at each assessment, even if no verbal output was observed on the first picture
- Pictures presented in counter balanced order at each assessment

Scoring Procedures

- Audio recording of each picture description transcribed verbatim
- Transcription and scoring completed by trained research assistant
- To calculate percentage of correct information units (%IUs):
    - Procedures used by Wright and Capilouto (2012)

- Each transcription assessed for total information units, “defined as a word that was intelligible, relevant, accurate, and informative relative to the stimulus” (p. 662)
- Each transcription also assessed for total words
  - Intelligible
  - excluded if they were filler words or considered commentary on the stimulus/task
- Total words divided by total information units, and multiplied by 100 to calculate the %IU.

- To calculate words per minute (WPM):
  - Each sample was timed
  - Intelligible words per minute calculated by dividing the minutes spoken by the total words.

Appendix F: Picture Naming

Instructions: Participant was instructed that he or she would see individual pictures and they were to tell the examiner the name of the each picture.

Pictures Used

Set 1 ***24 Hours***	***Set 2*** ***1 Week***	***Set 3*** ***2 Weeks***	***Set 4*** ***3 Months***
Wagon	Baby	Thermometer	Rake
Monkey	Scissors	Piano	Drum
Spoon	Tent	Queen	Table
Ring	Squirrel	Butterfly	Pig
Hamer	Foot	Sandwich	Camera
Crown	Candle	Bone	Flower
Ghost	Leaf	King	Cane
Turkey	Pillow	Vest	House
Hat	Bread	Skull	Duck
Pumpkin	Owl	Horse	Apple

Data Collection

- Ten individual pictures were presented at each assessment
- Responses were audio recorded
- Same set of pictures was used for each participant at the corresponding assessment
- Each stimulus was provided for 10 seconds without any prompts or cues
- Termination criteria: The task was terminated when there was no response on five consecutive pictures

Scoring Procedures

- Responses were initially scored from the audiotapes using the 16-point multidimensional scoring system from the Porch Index for Communication Ability (PICA) (Porch, 1967) by a highly experienced clinician trained in use of the system. Since the PICA scoring system is descriptive rather than ordinal, it was felt it might provide a more sensitive indicator of naming ability. However, many of the participants were unable to name pictures accurately or respond to the task. Examination of the naming data revealed there was no advantage to scoring responses with the PICA system and a post-hoc decision was made to score naming responses right or wrong. A percentage of naming accuracy on the task was calculated for each subject.

Appendix G: Procedures/Script for Data Collection

Subject: _____

Date of completion: _____

Time after stroke (circle one): w/i 24 hours 1 week 2 weeks 3 months

"I am going to ask you some questions, look at some pictures, and say some things. I am going to turn on the audio recorder now."

- Turn on recorder. Place microphone 6 inches from patient's mouth.

"I am going to ask you some questions. Try to answer as best as you can."

- Circle whether the subject is able to answer. If the subject is nonverbal and unable to state name or date of birth, discontinue the rest of the questions.
- Complete Short Portable Mental Status Questionnaire

<u>Vision and Hearing Screening (do only on initial timepoint)</u>

"Now I'm going to test your vision."

- Use vision screening task

"Now I'm going to test your hearing."

- Use OAE to screen hearing in both ears if participant is non-verbal
- Use CID Everyday Speech Sentences if participant is verbal

<u>Do at each timepoint</u>

"I'd like you to try to repeat some things after me."

1. Present digit recall task
    - "I will read you a list of numbers. I want you to repeat the numbers as best as possible."
    - If participant demonstrates error on 5 consecutive stimuli, discontinue task

2. Present polysyllabic words
    - "I will say some words one at a time. I was you to repeat the word the best that you can."
    - If participant is unable respond on 5 consecutive words, discontinue task

"Now I would like you to look at this picture and tell me about it. Try to use sentences and tell me what you see happening."

- Provide the cookie theft and the picnic scene picture for the patient to describe.
- Allow one minute for participant to respond
- Note which picture was presented first, alternate on assessments using data collection chart

"I will show you some pictures and I want you to tell me the name of each picture."

- Philadelphia Naming Test
    - Practice items x 3 first- without recorder on
    - Use the PNT30a or 30b in sets of 10
        - Use the set denoted for each assessment
    - Allow 10 seconds with each picture. Do not provide prompts. Only provide general feedback "you're doing fine"
    - If the subject is unable to produce any speech on 5 consecutive stimuli, discontinue naming testing.

<u>At three month timepoint</u>

Also provide QoL scale

Appendix H SAQOL-39

Name/ID:_____ **d.o.b.:**_____ **Δ:**_____
Date:_____

SAQOL-39g Scoring Sheet

DURING THE PAST WEEK (Repeat as in SAQOL-39)

Item ID	How much trouble did you have (Repeat before each item or as necessary)	Couldn't do it at all	A lot of trouble	Some trouble	A little trouble	No trouble at all	Domain scores		
							Physical	Comm.	Psycho-social
SC1.	preparing food?	1	2	3	4	5			
SC4.	getting dressed?	1	2	3	4	5			
SC5.	taking a bath or shower?	1	2	3	4	5			
M1.	walking? (If respondent can't walk, circle 1 and go	1	2	3	4	5			
M4.	keeping your balance when bending over or reaching?	1	2	3	4	5			
M6.	climbing stairs?	1	2	3	4	5			
M7.	walking without stopping to rest or using a wheelchair without stopping to rest?	1	2	3	4	5			
M8.	standing?	1	2	3	4	5			
M9.	getting out of a chair?	1	2	3	4	5			
W1.	doing daily work around the house?	1	2	3	4	5			
W2.	finishing jobs that you started?	1	2	3	4	5			
UE1.	writing or typing, *i.e. using your hand to write or type*?	1	2	3	4	5			
UE2.	putting on socks?	1	2	3	4	5			

UE4.	doing buttons?	1	2	3	4	5			
UE5.	doing a zip?	1	2	3	4	5			
UE6.	opening a jar?	1	2	3	4	5			
L2.	speaking?	1	2	3	4	5			
L3	speaking clearly enough to use the	1	2	3	4	5			
L5.	getting other people to understand you?	1	2	3	4	5			
L6.	finding the word you wanted to say?	1	2	3	4	5			
L7.	getting other people to understand you even when you repeated yourself?	1	2	3	4	5			

DURING THE PAST WEEK:

Item ID	Did you (Repeat before each item or as necessary)	Definitely yes	Mostly yes	Not sure	Mostly no	Definitely no	**Physical**	**Comm.**	**Psycho-social**
T4.	have to write things down to remember them, *(or ask somebody else to write things down for you to remember)?*	1	2	3	4	5			
T5.	find it hard to make decisions?	1	2	3	4	5			
P1.	feel irritable?	1	2	3	4	5			
P3.	feel that your personality has changed?	1	2	3	4	5			

MD2.	feel discouraged about your future?	1	2	3	4	5			
MD3.	have no interest in other people or activities?	1	2	3	4	5			
MD6.	feel withdrawn from other people?	1	2	3	4	5			
MD7.	have little confidence in yourself?	1	2	3	4	5			
E2.	feel tired most of the time?	1	2	3	4	5			
E3.	have to stop and rest often during the day?	1	2	3	4	5			
E4.	feel too tired to do what you wanted to do?	1	2	3	4	5			
FR7.	feel that you were a burden to your family?	1	2	3	4	5			
FR9.	feel that your language problems interfered with your family life?	1	2	3	4	5			
SR1.	go out less often than you would like?	1	2	3	4	5			
SR4.	do your hobbies and recreation less often than you would like?	1	2	3	4	5			
SR5.	see your friends less often than you would like?	1	2	3	4	5			

SR7.	feel that your physical condition interfered with your social life?	1	2	3	4	5			
SR8.	feel that your language problems interfered with your social life?	1	2	3	4	5			
	SAQOL-39g Mean score	Add all items and divide by 39							
	Physical score	(SC items + M items + W items + UE items) / 16							
	Communication score	(L items + FR9 + SR8) / 7							
	Psychosocial score	(T items + P items + MD items + E items + FR7 + SR1+SR4+SR5+SR7) / 16							

1. During administration: For each item, circle number that correspondents to respondent's choice
2. To calculate domain scores: Transfer each number to shaded area in same row. Average shaded boxes per column to calculate domain scores

Appendix I.1: Demographic and Medical Information- within 24 hours

Subject Number: _____

DOB: _____ Age: _____ Gender (Circle one): M F

Race: _____

Level of education: _____

Stroke Location: _____ Hours/days post onset: _____

Lesion Size: _____

Time from onset to initiation of tPA: _____

Ambulation at time of d/c from acute care (Circle one)

Non-ambulatory With two person assist With one person assist With equipment Independent

Medications

_____
_____
_____
_____
_____

Co-morbidities

_____
_____
_____
_____
_____
_____

NIHSS scores (for daily scores- enter lowest for each day)

On admission- prior to intervention	
First NIHSS 24 hours after intervention	

Appendix I.2: Demographic and Medical Information- 1 week

Subject Number: _____

DOB: _____ Age: _____ Gender (Circle one): M F

Stroke Location: _____ Hours/days post onset: _____

Amount of SLP intervention

Total Hours: _____

Number of days: _____

Amount of PT intervention

Total Hours: _____

Number of days: _____

Amount of OT intervention

Total Hours: _____

Number of days: _____

Ambulation abilities at time of evaluation (Circle one)

Non-ambulatory With two person assist With one person assist With equipment Independent

NIHSS scores (for daily scores- enter lowest for each day)

On admission- prior to intervention	
First NIHSS 24 hours after intervention	
On discharge from acute care	

Appendix I.3: Demographic and Medical Information- 2 week timepoint

Subject Number: _____

DOB: _____ Age: _____ Gender (Circle one): M F

Stroke Location: _____ Hours/days post onset: _____

Amount of SLP intervention

Total Hours: _____

Number of days: _____

Amount of PT intervention

Total Hours: _____

Number of days: _____

Amount of OT intervention

Total Hours: _____

Number of days: _____

Ambulation abilities at time of evaluation (Circle one)

Non-ambulatory With two person assist With one person assist With equipment Independent

Appendix I.4: Demographic and Medical Information-3 month timepoint

Subject Number: _____

DOB: _____ Age: _____ Gender (Circle one): M F

Stroke Location: _____ Hours/days post onset: _____

Amount of SLP intervention

Total Hours: _____

Number of days: _____

Amount of PT intervention

Total Hours: _____

Number of days: _____

Amount of OT intervention

Total Hours: _____

Number of days: _____

Ambulation abilities at time of evaluation (Circle one)

Non-ambulatory With two person assist With one person assist With equipment Independent

Appendix J: Charlson Comorbidity Index (CCI)

Diagnosis	Weight
Myocardial Infarction	1
Congestive Heart Failure	1
Peripheral Vascular Disease	1
Dementia	1
Chronic Pulmonary Disease	1
Connective Tissue Disease	1
Ulcer Disease	1
Mild Liver Disease	1
Diabetes	1
Diabetes with End organ damage	2
Moderate or Severe Renal Disease	2
Non-metastatic solid tumor	2
Leukemia	2
Lyphoma, Multiple myeloma	2
Metastatic Tumor	6
AIDS	6

Appendix K: National Institute of Health Stroke Scale

1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____

6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a.** **Left Leg** **6b. Right Leg**	_____ _____
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____

9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____
11. **Extinction and Inattention (formerly Neglect):** Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are or extinction to bilateral simultaneous stimulation in one _____ normal, the score is normal. If the patient has aphasia but does of the sensory modalities. appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** 2 = **Profound hemi-inattention or extinction to more than one modality**	

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Curriculum Vitae

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Place of Birth: Barren County, Kentucky

Education

Bachelor of Science, Communication Disorders; University of Kentucky May 2001

Summa Cum Laude

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Master of Science, Speech Language Pathology; University of Kentucky May 2003

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Academic Appointments

February 2008-August 2017: ***Assistant Professor, Clinical Services Director***

University of Kentucky College of Health Sciences

Professional Experiences

September 2017-Present: ***UK HealthCare Rehabilitation Supervisor, Speech Language Pathology***

University of Kentucky

November 2005-February 2008: ***Director of Rehabilitation***

Mayfair Manor; Lexington, KY

May 2003-November 2005: ***Speech Language Pathologist***

Healthcare Therapy Services, Inc.; Louisville, KY and Lexington, KY

Professional Awards

ASHA Award for Continuing Education Recipient, 2010

ASHA Award for Continuing Education Recipient, 2014

ASHA Award for Continuing Education Recipient, 2017

AB-SSD, Board Certified Specialty in Swallow and Swallowing Disorders, 2015

Publications

Danzl, M., Harrison, A., Hunter, E., Kuperstein, J., Sylvia, V., Maddy, K., Campbell, S. (2015). "A lot of things passed me by": Rural stroke survivors' and caregivers' experience of receiving education from healthcare providers. Journal of Rural Health, 32, 13-24.

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