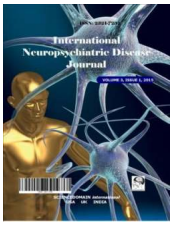

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Potential of Stimulants to Augment Rehabilitation in the Acute Stroke Setting: Preliminary Support

Jenny M. Ngo[1], Michael Korsmo[1], Karen C. Albright[2,3], Mansi M. Jhaveri[4,5], Ramy E. I. Khoury[1] and Sheryl Martin-Schild[1*]

[1]Department of Neurology, Tulane University Hospital, New Orleans, LA 70112, United States.
[2]Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Alabama, United States.
[3]Geriatric Research, Education, and Clinical Center (GRECC), Birmingham Veteran Affairs, Birmingham, Alabama 35233 United States.
[4]Department of Physical Medicine and Rehabilitation, University of Texas Health Sciences Center at Houston, Houston, Texas 77030, United States.
[5]Department of Neurology, University of Texas Health Sciences Center at Houston, Houston, Texas 77030, United States.

Authors' contributions

This work was carried out in collaboration with all authors. Author JMN wrote the Institutional Review Board protocol, collected data, and wrote the first draft of the manuscript. Author MK managed data collection and revision of subsequent manuscripts. Author KCA designed the pilot study, performed analysis on the preliminary work, and revised the manuscript. Author MMJ reviewed patient cases and edited subsequent manuscripts. Author RELK is the board certified neurologist who reviewed all data that was collected, reviewed each of the patient cases presented, and revised subsequent manuscripts. Author SMS is the board certified vascular neurologist who reviewed all data that was collected, reviewed each of the patient cases presented, reviewed the final manuscript, and made substantial changes to the final version of the manuscript. All authors read and approved the final manuscript.

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Case Study

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**Corresponding author: E-mail: jngo@tulane.edu, smartin2@tulane.edu;*

ABSTRACT

Aims: The objective of these case studies is to explore the possibility of using neurostimulants during the acute stage of stroke to facilitate effective rehabilitation of patients with severe strokes.
Presentation of Cases: In Case 1, methylphenidate was administered to a 63 year old woman with a left anterior cerebral artery infarct who was discharged to inpatient rehabilitation, rather than original recommendation of skilled nursing facility, prior to returning home. In Case 2, modafinil was administered to a 56 year old man with a left middle cerebral artery infarct who was discharged to inpatient rehabilitation prior to returning home. In Case 3, modafinil was administered to a 66 year old man with a left middle cerebral arery infarct who was discharged to inpatient rehabilitation. In Case 4, modafinil and methylphenidate were co-administered to a patient with a hypertensive intracerebral hemorrhage who experienced an adverse event possibly related to neurostimulants resulting in discontinuation. She was discharged to inpatient rehabilitation and subsequently to a skilled nursing facility.
Discussion: All cases initially presented to therapists with barriers to inpatient rehabilitation. Following neurostimulant administration, therapies recommended discharge to inpatient rehabilitation facility due to improvement in initial barriers. Three out of the four cases tolerated the neurostimulant well, while one case required discontinuation due to an adverse event.
Conclusion: Patients with severe strokes are less likely to meet criteria for inpatient rehabilitation. Depressed consciousness and limited attention are major barriers for which neurostimulants may be of benefit in the acute post-stroke setting. Administration of neurostimulants may improve participation in therapy, thus increasing qualification for inpatient rehabilitation, and ultimately accelerate recovery. Safety data in this population during the acute stage of stroke are lacking.

Keywords: Ischemic stroke; intracerebral hemorrhage; neurostimulant; modafinil; methylphenidate; inpatient rehabilitation.

ABBREVIATIONS

AIS: Acute Ischemic Stroke; ICH: Intracerebral Hemorrhage; mRS: Modified Rankin Scale; GCS: Glasgow Coma Scale; NIHSS: National Institute of Health Stroke Scale; SLP: Speech Language Pathology; PT: Physical Therapy; OT: Occupational Therapy; IPR: Inpatient Rehabilitation

1. INTRODUCTION

Stroke is the fifth most common cause of death and the leading cause of adult disability, affecting about 800,000 people in the United States each year [1]. Patients who undergo inpatient rehabilitation have better outcomes, including reduced mortality, less dependency, and a higher proportion discharged to home, but not all patients with stroke qualify [2].

Criteria for admission to inpatient rehabilitation include medical stability, functional deficits requiring two or more therapies (e.g., speech, occupational, physical), physical endurance to sit unsupported for at least one hour, ability to learn, and ability to tolerate therapy for three hours daily [2,3]. Dependent on location and severity of stroke, barriers for improvement of symptoms include decreased ability to attain and sustain consciousness. Individuals may have difficulty focusing and sustaining attention, which can interfere with information processing, performance on cognitive tasks, and rehabilitation participation [4,5].

Neurostimulants, such as methylphenidate and modafinil, have been shown to improve alertness and attention in patients with neurological disease, including patients with stroke [6,7,8]. Methylphenidate directly stimulates release of norepinephrine and dopamine in addition to blocking catecholamine reuptake with mild side effect profile and immediate onset of action [6]. Modafinil's mechanism of action is unknown but has been shown to be a norepinephrine agonist in the anterior hypothalamus [8]. Compared to methylphenidate, modafinil has a more favorable side effect profile, with less anxiety, hypertension, and tachycardia [8]. Methylphenidate and modafinil have demonstrated benefit for post-stroke depression and alertness, respectively [6,7,8]. Such rehabilitation pharmacology, while primarily studied in the subacute setting of patients who are in inpatient rehabilitation, may be of benefit during the acute

stage of stroke in order to increase participation and therefore acceptance to inpatient rehabilitation, giving them a better chance of returning home [6,9].

The following cases will explore four scenarios in which either methylphenidate, modafinil, or both were administered during the acute stage of stroke to patients not meeting inpatient rehab criteria due to deficits in level of consciousness and/or attention as documented by one or more therapy disciplines (speech and language, occupational, and physical therapists). Choice of neurostimulant was individual physician choice with considered factors of cost/insurance (favoring methylphenidate), concurrent depression (favoring methylphenidate), and co-morbidities (favoring modafinil).

2. PRESENTATION OF CASES

2.1 Methylphenidate during a Post-Acute Ischemic Stroke

Case 1 is a 63 year old African-American woman with a history of hypertension, diabetes mellitus, occasional alcohol use, and no reported tobacco or illicit drug use who presented with aphasia and right-sided weakness. At baseline she was completely independent. According to the most commonly used functional outcome measure for stroke, the modified Rankin Scale score (mRS), she is a zero (range zero [no symptoms] to six [deceased]).

On arrival her NIH stroke scale score (NIHSS), the most commonly used tool to quantify the degree of impairment in stroke, was a four. Scores less than 5 are considered minor, 5-15 moderate, 16-20 moderate to severe, and >20 severe strokes [10]. Imaging revealed a subacute distal left anterior cerebral artery infarction. The patient's NIHSS worsened (i.e., neurological deterioration) in the first 24-hour period, leaving her with an NIHSS of 10, secondary to stroke progression.

Initial therapy evaluations indicated the following barriers to inpatient rehabilitation (IPR). Occupational therapy (OT) documented that she required increased time to arouse. Physical therapy (PT) documented that consistent cueing was necessary for wakefulness. Ten days after the OT evaluation and eight days after the PT evaluation, methylphenidate (20 mg daily the first day followed by 10 mg daily) was administered. On day two of neurostimulant administration, therapy recommended discharge to IPR due to improved alertness and attention.

Methylphenidate was well-tolerated and continued through discharge. After a thirteen day hospital stay, the patient was discharged to IPR with a NIHSS of 3 and a mRS score of 4. Following her 14 days in IPR, she was discharged home.

2.2 Modafinil during a Post-Acute Ischemic Stroke

Case 2 is a 56 year old Caucasian man with a history of coronary artery disease status post-coronary artery bypass grafting, radiculopathic pain, occasional alcohol use and a current smoker. He presented with sudden onset inability to speak and right-sided weakness noted upon waking. Prior level to this event, he was completely independent (mRS = 0).

On admission the patient had an NIHSS of 16. Imaging revealed a left middle cerebral artery distribution ischemic stroke with occlusion of the left common carotid artery to internal carotid artery at its origin.

Initial therapy evaluations documented the following barriers to IPR. Speech language pathology (SLP) documented that the patient was only able to maintain a wakeful state for 2-3 minutes at a time and required verbal and tactile cues for participation. OT documented that the patient was distractible by external stimuli. Five days after SLP's and six days after OT's initial evaluations, modafinil (200 mg daily) administration began. On the fourth day of neurostimulant administration, therapy recommended discharge to IPR due to improved wakefulness and attention.

Modafinil was well-tolerated. After ten days on the inpatient stroke service, his NIHSS was 13 with a mRS score of 5. He was discharged to IPR where he stayed for twenty-two days prior to being discharged home.

2.3 Modafinil during a Post- Acute Ischemic Stroke in an Elderly Patient

Case 3 is a 66 year old Caucasian man with a history of atrial fibrillation, multiple myeloma reportedly in remission, hypertension, and reported tobacco, alcohol, and cocaine use. He

presented with global aphasia and right hemiparesis. Prior to his stroke he was completely independent (mRS = 0).

On arrival he had a NIHSS score of 22. Imaging revealed a left middle cerebral artery territory subacute ischemic infarct. Initial therapy evaluations indicated the following barriers to inpatient rehabilitation: SLP documented that patient was falling asleep within one minute without stimulation and lacked responsiveness and alertness. PT documented that patient was unable to awaken and lacked responsiveness. The patient was started on modafinil (200 mg daily). On day two of neurostimulant therapy, SLP and PT recommended discharge to inpatient rehabilitation due to improved alertness and wakefulness.

Modafinil was well-tolerated. After a twenty-one day hospital stay, his discharge NIHSS was 14 and his mRS score was 4. He was discharged to IPR where he stayed for twenty-nine days prior to being discharged home.

2.4 Methylphenidate and Modafinil during an Acute Post-Intracerebral Hemorrhage Discontinued after an Adverse Event

Case 4 is a 68 year old Caucasian woman with a history of hypertension with no reported tobacco, alcohol, or illicit drug use. The patient presented immobile after two days of left-sided weakness. Her baseline function was classified as moderately severe disability. She was unable to walk without assistance and unable to attend to own bodily needs without assistance (mRS = 4).

On exam, she demonstrated a decreased level of consciousness and scored 19 on initial her NIHSS. Imaging revealed an acute intraparenchymal hemorrhage extending from the right centrum semiovale to the right thalamus with surrounding edema and intraventricular extension. A volume of 13cc of intraventricular hemorrhage with 7 mm leftward midline shift was noted. Twenty-four hours later, the patient experienced neuroworsening (NIHSS 22) and required an external ventricular drain placement for her obstructive hydrocephalus.

Initial therapy evaluations were delayed by twelve days due to the patient being medically unstable, intubated, and sedated. Modafinil (200 mg daily) and later methylphenidate (20 mg daily) were administered before the patient was deemed appropriate for therapy evaluations. Evaluations indicated the following barriers to IPR: OT documented drowsiness and impaired attention. PT documented an obtunded state that impaired learning. After eighteen days of treatment with modafinil and ten days of treatment with methylphenidate, PT and OT recommended IPR due to increased arousal and ability to follow commands. Unfortunately, before the patient was medically ready for discharge, she developed new onset paroxysmal atrial fibrillation leading to discontinuation in the neurostimulants. At the time of discharge, she was drowsy with an NIHSS of 19 and a mRS of 5. After a forty-eight day hospital stay, the patient was discharged to IPR where she stayed for twenty-two days prior to being admitted to a skilled nursing facility.

3. DISCUSSION

These cases demonstrate the ability of neurostimulants to augment attention and level of consciousness in the acute post-stroke phase. By increasing alertness, neurostimulants have the potential to help stroke patients meet IPR criteria. All four patients presented with moderate-to-severe strokes. As commonly seen with this severity of stroke, there were initial barriers to IPR. Following treatment with methylphenidate, modafinil, or both, all four patients demonstrated improved participation resulting in upgraded recommendations for the next appropriate level of rehabilitation care. The first three cases highlight patients that tolerated neurostimulant treatment well, with subsequent discharge to IPR followed by discharge home. However, the patient in case 4 required neurostimulant discontinuation due to development of paroxysmal atrial fibrillation. Atrial fibrillation is associated with higher in-hospital mortality in the ischemic stroke population, particularly in patients with cardioembolic stroke subtype [11]. While it is not known whether the neurostimulant caused her atrial fibrillation, methylphenidate is associated with tachycardia. Case 4 illustrates that neurostimulants may not be tolerated by all acute stroke patients. Neurostimulants, particularly when administered to the elderly or in combination, may pose risk for some acute stroke patients. Thus, further study is necessary to establish the safety of FDA approved stimulants in patients with moderate-to-severe strokes in the acute stage.

These cases demonstrate an association between neurostimulant administrations, PT/OT rehabilitation recommendations for IPR, and discharge to inpatient rehabilitation. Prior studies of methylphenidate and modafinil in stroke patients were conducted in the rehabilitation setting—outside of the acute stage of stroke [6,9]. Neurostimulants may augment endogenous repair phenomena including angiogenesis, neurogenesis, and synaptic plasticity [12]. We believe that patients with moderate-to-severe stroke may benefit from a neurostimulant trial during the acute stroke stage in an effort to increase their level of alertness. Improved alertness, in turn, can increase their chances of being discharged to IPR. Currently we have no evidence to guide providers on this matter. Given this clinical equipoise, we feel that it is time for a randomized controlled trial testing neurostimulants in acute post-stroke patients. This trial would allow us to determine if treatment with neurostimulants increases the proportion of moderate-to-severe stroke patients discharged to IPR and then home. Optimal duration of administration would also need to be elucidated. If this simple intervention is proven to be safe and effective at increasing the proportion of moderate-to-severe stroke patients discharged to IPR, rather than to a nursing home, we could cut the healthcare costs of stroke by hundreds of millions of dollars annually and help to ensure that patients with stroke return home.

4. CONCLUSION

Patients with moderate to severe strokes are less likely to meet criteria for inpatient rehabilitation and more likely to require prolonged hospital stay with subsequent custodial care. Studies show that a stroke patient's best chance at an optimal outcome is via aggressive inpatient rehabilitation; however, reduced levels of consciousness and attention serve as major barriers to getting the necessary IPR recommendations from PT and OT. FDA approved neurostimulants, such as methylphenidate and modafinil, used in the post-acute stroke setting have the potential to help remove these IPR barriers and ultimately return stroke patients to their homes.

CONSENT

The Tulane Institutional Review Board granted a waiver of informed consent.

ETHICAL APPROVAL

The retrospective chart review was approved by the institutional review board at the Tulane University (IRB protocol number 631421-1).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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