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RESEARCH ARTICLE

Evaluation of Outcomes in Patients Receiving Modafinil to Improve Alertness after Traumatic Brain Injury

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ABSTRACT

Background: Modafinil is used for improving wakefulness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder. The goal of this study is to evaluate alertness and participation in physical therapy and occupational therapy in patients with a first-time diagnosis of traumatic brain injury using modafinil.

Methods: This was a single-center, retrospective, chart review, cohort study of Ochsner Medical Center patients from January 2016 to December 2018. Patients included in the study were 18 years of age or older who were hospitalized due to a traumatic brain injury and received modafinil either by mouth, nasogastric, or enteral feeding tube to help improve alertness. The primary outcome is the change in Glasgow Coma Scale (GCS) score from baseline to 72 hours after initiating modafinil.

Results: One-hundred and Forty patients were included with a mean age of 67.8 years and 59.3% were male. The majority of the patients (52.9 %) were predominantly patients who suffered ischemic stroke. The mean change in GCS score in 72 hours was +0.35 (95% CI [-0.16, 0.88], p=0.177). One of the secondary endpoints was the mean change in course of therapy GCS score which showed significant improvement in neurological function after initiation of modafinil: +1.22 (95% CI [0.64, 1.80], p=0.0001). The percent physical therapy/occupational therapy (PT/OT) session participation at 72-hour post-modafinil initiation was 96.7% compared to 95.7% during the course of therapy. The correlation between increase in GCS score and percent PT/OT therapy session participation was analyzed at 72 hours and throughout the course of therapy, which revealed no significant association (r=0.14 [p=0.0911] and -0.06 [p=0.4881], respectively).

Conclusion: Our study did not find a significant increase in the mean change of GCS score at 72 hours of modafinil use. Although, there were high percentage of patients participated in PT/OT in 72 hours and course of therapy (96.7% and 95.7%), there was no significant statistical correlation between increase in GCS score and PT/OT participation. Randomized studies are needed to further assess the impact of modafinil for treating traumatic brain injury associated sleep-wake disturbances while considering factors such as medication initiation time, appropriate dosage, GCS score, and long-term outcomes.

Keywords: Modafinil; traumatic brain injury; sleep-wake disturbances; stroke; alertness; excessive daytime sleepiness

INTRODUCTION

Around 2.5 million people in the United States suffer from a traumatic brain injury (TBI) annually that usually results in hospitalization. One major side effect that accompanies TBIs is sleep wake disturbances[1-4].30-70% of TBI patients suffer from sleep wake disturbances (SWDs), which can continue for years after their diagnosis, significantly decreasing their quality of life[4,5]. Multiple physiological pathways are responsible for these SWDs with the most prominent pathway being a significant decrease in serotonergic and noradrenergic neurons. Other contributing factors include a decreased production of melatonin, diminished release of orexin/hypocretin (ORX) neurons, and upregulation of glutamate signaling. Normal regulation of these neurons promotes and regulate arousal in patients without TBIs[4,6].

As a result of the dysregulation of numerous neurological pathways, rehabilitation of patients with TBIs is tremendously affected. Studies show that patients that experience prolonged impaired consciousness can delay rehabilitation and recovery as patients must be awake and alert to participate in physical and occupational therapy[7]. These sleep disturbances have also been directly linked to an increase in hospital stays in rehabilitation patients[8,9]. To combat the effects of SWDs on patient recovery, early participation in physical activity and rehabilitation can decrease the harmful effects of increased bed rest such as musculoskeletal loss[10]. In addition to participating in early mobilization, medications such as modafinil may help stimulate wakefulness in patients in order for them to participate in physical therapy[11]. Elkbuli et al. compared early physical therapy (PT) initiation versus late initiation in patients with or without traumatic brain injury and found decreased complications and shorter hospital and ICU length of stays (LOS) among patients with traumatic brain injury[12].

The Glasgow Coma Scale (GCS), Coma Recovery Scale-Revised (CRS-R), and Disability Rating Scale (DRS) are a few of the many different scales that are used to classify alertness in TBI patients. The GCS is one of the more common tools that is used to assess the severity of a TBI. Patients' results are based on how well they respond to the motor, verbal, and eye-opening tests. Severe brain injuries are classified by a score of 8 or less. Moderate injury has a GCS score of 9-12, and a mild injury has a score of 13-15[13]. The Glasgow Coma Scale score has also been found to be a valid predictor of mortality, which can be especially important upon hospital admission of a TBI[14]. The lower GCS scores have also been strongly associated with the need for more sleep[15].

Modafinil is FDA approved for the treatment of narcolepsy associated excessive daytime sleepiness, obstructive sleep apnea, and shift work sleep disorder[11,16]. It has multiple mechanisms of actions with significant effects on serotonin, catecholamines, glutamate, gamma amino-butyric acid (GABA), orexin, and histamine systems. Compared to other drugs with similar effects such as amphetamines, it is highly tolerable with a low risk of abuse. Studies have shown different findings on the effects of modafinil on dopamine receptors, but all of them insinuate that at least some of its effect is through synaptic dopamine mediation with its mechanisms being much different than amphetamines. The effects of modafinil on the increased levels of serotonin, glutamate, and histamine levels are secondary to its dopaminergic effects, which is mostly responsible for the wakefulness effects[17-21].

Several small studies have examined modafinil's effect on wakefulness in TBI patients and in animal studies, but the most recent study was a prospective, single center, placebo-controlled, double-blind, randomized crossover trial by Visser et al[22]. Data were retrieved from the Modafinil In Debilitating Fatigue After Stroke (MIDAS) trial[23]. This study included 28 individuals who struggled with fatigue after having a stroke. Improvements in fatigue were measured by resting-state functional connectivity (rsFC). The study's results showed that the administration of modafinil strongly correlated with an improvement in rsFC. Although modafinil was not proven to be the direct cause of the increased rsFC, the neuroimaging from this study suggests a potential causal relationship between the two factors[23]. Another prospective, double-blind, randomized, placebo-controlled study conducted by Kaiser et al. found that modafinil had no effect on posttraumatic fatigue although the study did find that modafinil increased wakefulness[24]. Another prospective, double-blind study also supports that modafinil does not improve fatigue, but it does improve sleepiness, which was measured by the Maintenance of Wakefulness Test and Epworth Sleepiness Scale[25,26]. Dhamapurkar et al. compared the effects of modafinil using CRS-R method in a two-arm retrospective study involving 12 TBI patients and 12 non-TBI patients. The study

found that modafinil was more beneficial to TBI patients than non-TBI patients[27].

Modafinil's use as an off-label treatment to improve wakefulness in patients with TBI requires further exploration. To our knowledge, previous studies that have looked at this relationship have been smaller and have not looked into the correlation of GCS score improvement with clinical outcomes such as the ability to participate in rehabilitation during the initial hospitalization after a TBI. The goal of this retrospective, single-center study is to evaluate the mean change at 72 hours and in course of therapy (COT) GCS score after modafinil initiation and to correlate the change in GCS score with participation in physical therapy (PT) and occupational therapy (OT) among TBI patients receiving modafinil during the first hospitalization.

METHODS

Study Design

This study was a single-center, retrospective, single-group, cohort study conducted at Ochsner Medical Center, New Orleans, LA. All patients admitted to Ochsner Medical Center between the dates of January 2016 and December 2018 for a TBI and received one or more doses of modafinil to increase alertness were screened. International Classification Diseases (ICD) 9th revision and ICD 10th revision diagnosis codes (see table 1) were used to identify the patients. The Xavier University of Louisiana Institutional Review Board and the Ochsner Medical Center Research Review Committee approved this study. Informed consent waiver was granted because of the retrospective nature of this study.

Table 1: ICD diagnosis codes

ICD 9 Diagnosis Codes for TBI	ICD 10 Diagnosis Codes for TBI
• 850 Concussion • 851 Cerebral, cerebellar, or brain stem contusion or laceration • 852 Subarachnoid, subdural, or extradural hemorrhage following injury • 853 Other and unspecified intracranial hemorrhage following injury • 854 Intracranial injury of other and unspecified nature	• S06.0 Concussion • S06.1 Traumatic cerebral edema • S06.2 Diffuse traumatic brain injury • S06.3 Focal traumatic brain injury • S06.4 Epidural hemorrhage • S06.5 Traumatic subdural hemorrhage • S06.6 Traumatic subarachnoid hemorrhage • S06.8 Other specified intracranial injuries • S06.9 Unspecified intracranial injury

Inclusion and Exclusion Criteria

The inclusion criteria for the study were as follows: primary diagnosis for hospitalization was a TBI, 18 years of age or older, modafinil used to improve alertness, and able to take medications by mouth or via nasogastric or enteral feeding tubes. Patients were excluded from the study if modafinil was used for any indications other than increasing alertness, had pre-existing neurologic injuries prior to the TBI (prior TBI, stroke, and brain tumor), had modafinil allergy, modafinil dose was administered less than 72 hours for TBI treatment, had bowel obstruction, received end-of-life care/brain dead, were pregnant, and if the patient had missing GCS score data. Patients with the following baseline comorbidities were also excluded: baseline idiopathic hypersomnia, narcolepsy, seizures, obstructive sleep apnea (OSA), multiple sclerosis (MS) related fatigue, Parkinson's disease (PD), Alzheimer's disease, and psychological conditions.

Data Collection

All patient data were obtained from Ochsner Medical Center electronic medical records. The following demographic data were collected: age, sex, race, height, weight, admission date, discharge date. We also collected baseline comorbid conditions (hypertension, MS, depression, OSA, PD, seizures, psychiatric conditions), GCS score (on admission, baseline, 72 hours, modafinil discontinuation, and at discharge), duration of treatment in days, total modafinil dose (in milligrams) at 72 hours and during course of therapy (COT), intensive care unit (ICU) length of stay (LOS) in days, non-ICU LOS in days, total LOS in days, time from TBI to initiation of modafinil in days, wakefulness and PT/OT participation at 72 hours and COT, use of concurrent psychotropic medications that could affect study outcomes: antipsychotics, dopaminergic agents, anticonvulsants, anxiolytics, anticholinesterase inhibitors, antidepressants, benzodiazepines,

anticholinergics, sympathomimetics, antihistamines, NMDA receptor antagonist, and sedatives. The complete list of concurrent psychotropic medications can be found in Appendix 2.

Definitions

Admission GCS score was defined as the first GCS score documented after admission whereas baseline GCS score referred to the GCS score documented before modafinil initiation. COT GCS score was the change from baseline GCS score to discharge GCS score. Concurrent psychotropic medication was defined as a medication that was administered at least once during modafinil COT.

Outcomes

The primary outcome was the mean change in GCS score from baseline to 72 hours after the start of modafinil. The secondary outcomes include the mean change in the COT GCS score after the start of modafinil and the correlation between GCS and percent PT/OT session at 72 hour and through COT. The percentage of patient participation in PT/OT sessions at 72 hours and at discharge was also measured. Duration of treatment, total length of stay (LOS), intensive care unit (ICU) LOS, non-ICU LOS, time to modafinil initiation, the amount of modafinil given at 72 hours and discharge, type and severity of TBI, and concurrent psychotropic medications were also measured as secondary outcomes.

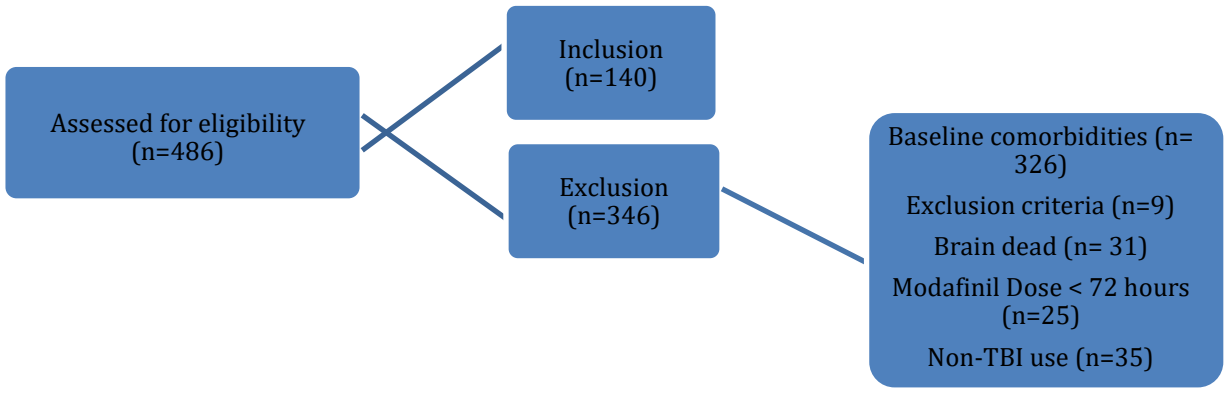
Statistical Analysis

For the baseline characteristics, a descriptive statistical analysis was used, and a two-tailed paired t-test was performed for the mean change in the GCS score. Time from TBI to the initiation of modafinil (within 72 hours and >72 hours), type of TBI or stroke (intracranial injury, concussion, hemorrhagic, or ischemic), and severity of TBI (mild, moderate, severe) were analyzed as subgroups. These subgroups were analyzed to compare the change in GCS score from baseline to 72 hours among groups using the Analysis of Variance (ANOVA) test. The change in GCS score was also compared between the groups that concurrently took psychotropic medications and those who did not. An alpha of less than 0.05 was considered statistically significant. STATA Statistical Software, Release 12. College Station, TX was used to perform the statistical analyses[28].

RESULTS

A total of 486 patients were hospitalized with a primary diagnosis of a TBI who received at least one dose of modafinil. Three hundred forty six were excluded from the study and the most common exclusion criteria were presence of baseline comorbidities (multiple sclerosis, idiopathic hypersomnia, narcolepsy, Alzheimer's disease, obstructive sleep apnea, Parkinson's disease, seizure disorder, depression), modafinil dose was administered less than 72 hours for TBI treatment, and modafinil was used as non-TBI indication (see figure 1).

Figure 1. Flow Chart



Baseline characteristics

The mean age of the patients was 68 years. Most patients were Caucasian (54.3%) or Black (37.9%) while 59.3% were male. Between the types of injuries among the patients, 52.9% had an ischemic stroke, 44.3% had a hemorrhagic stroke, and 3.6% had a concussion. The GCS score recorded before the initiation of modafinil revealed an even distribution of TBI severity categories: 38.6% were mild (GCS score 13-15), 31.4% were moderate (GCS score 9-12), and 30% were severe (GCS score ≤ 8). The majority of concurrent medications included sedatives (57.9%), anticonvulsants (48.6%), benzodiazepines (30.0%), sympathomimetics agents (28.6%), and antipsychotics (19.3%). (See table 2)

Table 2. Baseline characteristics

Baseline Characteristics	**Modafinil (n=140)**
Mean Age, years (range)	67.8 (26–98)
Male, n (%)	83 (59.3)
Female, n (%)	57 (40.7)
Race, n (%)	
Black	53 (37.9)
Caucasian	76 (54.3)
Other	11 (7.9)
Type of TBI, n (%)	
Concussion	5 (3.6)
Hemorrhagic stroke	62 (44.3)
Ischemic stroke	73 (52.1)
TBI Severity on admission based on GCS score, n (%)	
Mild (GCS score = 13 – 15)	54 (38.6)
Moderate (GCS score = 9 – 12)	44 (31.4)
Severe (GCS score ≤ 8)	42 (30)
Mean total LOS (days ± SD)	30.7 ± 17.3
ICU LOS (days ± SD)	19.2 ± 15.0
Non-ICU LOS (days)	11.5 ± 13.8
Time to step down or discharge (days)	11.6
Mean time to modafinil initiation (hours) (range)	307.4 (73 – 984)
Concurrent medications, n (%)*	
Anticonvulsants	68 (48.6)
Benzodiazepines	42 (30.0)
Anxiolytics	13 (9.3)

Sedatives	81 (57.9)
Antipsychotics	27 (19.3)
Anticholinergics	7 (5.0)
Antihistamines	6 (4.3)
Antidepressants	20 (14.3)
Sympathomimetics	40 (28.6)
Dopaminergic Agents	12 (8.6)
Acetylcholinergic Inhibitors	3 (2.1)
NMDA receptor antagonists	1 (0.7)

*No patients received NMDA receptor antagonists, other dopaminergic agents or acetylcholinesterase inhibitors. GCS = Glasgow Coma Scale/Score, LOS = Length of Stay, TBI = Traumatic Brain Injury

Outcomes

The mean change in 72 hours GCS score from baseline was +0.35 (95% CI [-0.16, 0.88], p = 0.177) which was not a statistically significant change. Although the mean change in 72 hours GCS score was not significant, the mean change in COT GCS score was statistically significant in the direction of improvement in neurological function, +1.22 (95% CI [0.64, 1.80] p = 0.001). The percent PT/OT session participation at 72-hour post-modafinil initiation was 96.7% compared to 95.7% during the COT. The correlation between GCS and PT/OT session was analyzed by the Spearman correlation at 72 hours and throughout the COT, which resulted in no significant association (r = 0.14 and – 0.06, p = 0.0911 and 0.4881), respectively.

Table 3. Results- Study Endpoints

GCS and PT/OT endpoints	**Mean (95% CI)**	**r**	**P value**
Primary endpoint (n = 140)			
Mean change in 72 hour GCS (72 hr GCS – baseline GCS)	+0.35 (-0.16, 0.88)		0.177
Secondary endpoints (n = 140)			
Mean change in COT GCS (COT GCS – baseline GCS)	+1.22 (0.64, 1.80)		0.0001
Correlation between GCS & PT/OT Session			
72- hour GCS and 72- hour % PT/OT session participation		0.14	0.0911
COT GCS and COT % PT/OT session participation		-0.06	0.4881
Additional endpoints			
Mean 72-hour %PT/OT session participation (SD, range), n = 110	96.7 (11.0, 33-100)		
Mean COT %PT/OT session participation (SD, range), n = 124	95.7 (12.0, 50-175)		

*r = correlation coefficient

The other secondary endpoints included time from TBI to modafinil initiation was 12.8 days and the mean modafinil COT per duration of treatment was 12.8 days. The mean total length of stay (LOS) for patients at the hospital was 30.8 days, the mean ICU LOS averaged to 19.2 days, and 11.6 days for the mean non-ICU LOS. Similarly, the average days patients stepped down from ICU to the non-ICU floor or discharged from the hospital was 11.6 days. Patients received a total of 2,258.3 mg of modafinil during the course of therapy (COT) and 480.7 mg of modafinil in the first 72 hours from admission.

Table 4. Results- Descriptive (n = 140).

Other secondary endpoints	
Mean time from TBI to modafinil initiation in days, (SD, range)	12.8 (8.2, 3-41)
Mean modafinil COT per duration of treatment in days (SD, range)	12.8 (16.7, 1-168)
Median modafinil total daily dose, mg (range) 72- hour modafinil dose Final COT (Discharge) modafinil dose	 500 (96-1600) 1400 (100-16600)
Baseline GCS score (at modafinil initiation), mean (SD, range)	10.7 (3.44, 3-15)
72- hour GCS score (post-modafinil initiation), mean (SD, range)	11.1 (3.17, 3-15)
Discharge GCS score, mean (SD, range)	11.9 (3.11, 3-15)
Total LOS in days, mean (SD, range) ICU LOS Non-ICU LOS	30.7 (17.3, 5-90) 19.2 (15.0, 0-65) 11.5 (13.8, 0-59)

COT = Course of Therapy, TBI = Traumatic Brain Injury

Table 5. Subgroup Analyses

Subgroup analyses	**Mean change in 72-hour GCS**	**P**
Admission TBI severity Mild (n=54) Moderate (n=44) Severe (n=42)	 +13.3 +9.95 +9.33	 .000
Concurrent psychotropic medication vs no psychotropic medication Anticonvulsants (n=68) vs none (n=72) Benzodiazepines (n=42) vs none (n=98) Sedatives (n=81) vs none (n=59) Antipsychotics (n=27) vs none (n=113) Anticholinergics (n=7) vs none (133) Antihistamines (n=6) vs none (n=134) Antidepressants (n=20) vs none (n=120) Anxiolytics (n=13) vs none (n=127) Sympathomimetics (n=40) vs none (n=100)	 +10.3 (vs +11.8) +10.3 (vs +11.4) +10.1 (vs +12.4) +12.3 (vs +10.8) +11.6 (vs +11.0) +10.8 (vs +11.1) +12.0 (vs +10.9) +9.15 (vs +11.3) +10.0 (vs +11.5)	 .005 .091 .000 .010 .667 .901 .124 .061 .008

DISCUSSION

Patients experiencing TBI of any severity experience decreased wakefulness, fatigue, and sleep fragmentation throughout their recovery. In both the acute and chronic phases of TBI, sleep-wake disturbances vary among patients, and treatment decisions are often dependent on GCS scores and PT/OT improvement. GCS measurements from baseline, 72 hours, discontinuation, and discharge assist in assessment of patient progression and treatment plan. Symptom-directed therapy is usually initiated quickly following admission to improve patients' chances of functional recovery and decrease long term consequences. Despite the knowledge on different therapeutic approaches for the care of patients following a TBI, there is need to study additional medications and their impact on surrogate markers of neurological and physical improvement. Given the dearth of clinical data on the impact of modafinil on clinical outcomes in patients with TBI, our study makes notable contributions by examining the impact of modafinil on clinical outcomes in patients with TBI.

In this single-center retrospective study of patients with a TBI (including ischemic and hemorrhagic stroke), we analyzed the impact of modafinil on the GCS score, as well as other clinical outcomes such as participation in PT and OT sessions. We hypothesized that modafinil would improve alertness post-TBI at 72 hours, indicated by an increase in the mean GCS score, and that modafinil would increase the percentage of patients with a TBI who participate in PT and OT sessions. In our study, we found a slight increase of GCS score at 72 hours, but it was not statistically significant. However, the increase in GCS score at discharge was found to be statistically significant denoting improvement of neurological function with modafinil beyond 72 hours $p = 0.0001$. Our study result is comparable to the Dhamapurkar et al. trial, which illustrated a statistically significant increase in neurocognitive functioning following modafinil initiation[27]. In the study by Dhamapurkar et al., the Wessex Head Injury Matrix (WHIM) - a measure to monitor recovery of cognitive function, communication skills, and social interaction – was significantly increased in TBI patients receiving modafinil compared to their baseline WHIM score ($p < 0.004$). Similar to our study finding, the improved WHIM scores (a surrogate measure of cognitive function) following modafinil use in TBI parallel the statistically significant improvement in GCS scoring upon discharge (COT GCS) in our study's TBI patient population, demonstrating increased neurocognitive functioning with modafinil use in TBI[27]. Lastly, the correlation between the GCS score and percentage of PT/OT session participation at 72 hours and discharge was not statistically significant.

Our study showed high levels of participation in PT/OT sessions during the 72-hour post-modafinil and during modafinil COT. This indicates that modafinil may provide some neurological improvement and facilitates patients' readiness for PT and OT participation. Although not entirely identical to the outcomes of PT or OT, a double-blind, randomized, placebo- controlled study by Kaiser et al. demonstrated modafinil effectiveness in treating posttraumatic excessive daytime sleepiness (EDS), but it had no effect on fatigue[24]. The Epworth Sleepiness Scale (ESS) was used to assess EDS in patients compared to placebo. The Kaiser et al. study shows that modafinil reduced EDS which is a necessary pre-requisite for participation in PT and/or OT activities.

In our study, most of the concurrently given medications were antipsychotics, anticonvulsants, benzodiazepines, and sedatives, which can cause additional sedation[29]. Antipsychotics are also dopamine antagonists that can potentially interfere with modafinil's putative dopamine mechanism of action[30]. This could be a confounding factor as to why the mean change of GCS score in 72 hours did not improve significantly. Despite these effects, patients receiving these medications were still included because these medications are often included in the standard regimen for TBI treatment. According to the Brain Trauma Foundation Guidelines for Management of Severe Traumatic Brain Injury, sedatives are commonly used as prophylaxis for intracranial hypertension, and anticonvulsants are used as prophylaxis for post-traumatic epilepsy. TBI patients are at high risk for both of these conditions[31].

Despite the lack of a significant increase in the GCS score at 72-hours post-modafinil initiation, one of the main strengths of our study was the increase in COT GCS score from baseline and the clinical improvements in our patients. The percent PT/OT session participation at 72-hour post-modafinil initiation was 96.7%. Although we did not find that there was a correlation between the changes in GCS score (at either 72 hours or COT) with percentage of PT/OT session participation, our patients experienced better outcomes with their increased PT/OT participation. A study conducted by Horn et al. found that patients who spent more

time in inpatient rehabilitation therapy sessions experienced better outcomes at discharge[32]. Additionally, we used GCS score to measure our primary outcome, which is a prominent tool used to measure the severity of TBIs[33]. There is no gold standard to assess the consciousness level in this population of patients, but GCS score has been shown to be a reliable predictor of mortality and recovery post-TBI[13,34,35].

Several limitations apply to our study. First, this study is a single-center retrospective design which impacts its external and internal validity. A single-center design decreases the external validity as our site might not reflect the true target population of patients. A major disadvantage of this study is its retrospective design, which could introduce incomplete or missing data which can reduce the internal validity of our study. Our study also lacked a control group (no modafinil treatment) to compare our study outcomes. The lack of a control group impacts the internal validity of our study and makes it challenging to ascertain if our observed outcomes were due to modafinil or were chance findings. Another limitation impacting the generalizability of our study was the makeup of the included TBI patients, which comprised of mostly non-classic TBI patients. Although we set out to study modafinil for TBI using ICD-9 and ICD-10 codes, we were unable to identify patients with classic TBI (focal or diffuse TBI), perhaps because our hospital is not a trauma center. Our TBI study population included hemorrhagic stroke, ischemic stroke, and concussion patients. We realize this population of TBI does not fit the classic TBI definition and we acknowledge this definition aberration as a limitation of our study. Additionally, our study sample size is relatively small at 140 patients which could increase our chance of type II errors and may have impacted our ability to detect statistically significant differences in our study outcomes. Furthermore, renal impairments were not taken into consideration, which could impact the effects of modafinil in some of our patients. In severe, chronic renal impairment, modafinil's inactive metabolite – modafinil acid increases 9-fold, significantly decreasing modafinil's effect[17]. Lastly, we were only able to observe the outcomes over a short period of time, as the average course of therapy was just 12.7 days. Therefore, it may be useful to study impact of modafinil treatment in TBI patients long-term, including days beyond their hospital discharge.

CONCLUSION

Although the mean change in 72-hour GCS score was not significantly increased, the mean change in COT GCS score was significantly increased which indicates potential improvement in the neurological function in patients with TBI who received modafinil. Although there were high percentage of patients that participated in PT/OT in 72 hours and COT (96.7% and 95.7%), the correlation analysis between PT/OT participation and GCS score rendered no statistical significance. Randomized studies are needed to further assess the impact of modafinil for treating TBI associated sleep-wake disturbances while considering factors such as medication initiation time, appropriate dosage, GCS score, and long-term outcomes.

Conflict of Interests

The author(s) have no conflicts of interest to declare.

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APPENDICES

Appendix 1: Concurrent Medications

Antipsychotics Droperidol Haloperidol Fluphenazine Pimozide Thiothixene Trifluoperazine Molindone Loxapine Chlorpromazine Mesoridazine Thioridazine Clozapine Olanzapine Quetiapine Risperidone Ziprasidone Melperon **Dopaminergic agents** Carbidopa/levodopa Bromocriptine Pergolide Pramipexole Ropinirole Selegiline **Anticonvulsants** Phenobarbital Clonazepam Primidone Topiramate	**Antidepressants** Amitriptyline Amoxapine Clomipramine Desipramine Doxepin Imipramine Maprotiline Notriptyline Trimipramine Protriptyline Isocarboxazid Phenelzine Tranylcypromine Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline Bupropion Mirtazapine Nefazodone Venlafaxine Duloxetine **Anxiolytics** Buspirone Chloral hydrate Zolpidem Zopiclone	**Benzodiazepines** Chlordiazepoxide Clonazepam Clorazepate Diazepam (valium) Flurazepam Estrazolam Lorazepam Temazepam Alprazolam Midazolam Oxazepam Triazepam **Anticholinesterase inhibitors** Donepezil Galantamine Rivastigmine **Anticholinergics** Atropine Benztropine Bepiriden Cyclopentolate Dicyclomine Glycopyrrolate Hyoscyamine Mepenzolate Methscopolamine Procyclidine Scopolamine Tolterodine Triheylpehidyl Trimethobenzamide	**Sympathomimetics** Methylphenidate Dexmethylphenidate Dextroamphetamine Dextroamphetamine Dextroamphetamine and racemic amphetamine Pemoline Phentermine Sibutramine Atomoxetine **Antihistamines** Promethazine **NMDA receptor antagonist** Memantine **Miscellaneous** Metoclopramide