Trauma Mon. 2019 January; 24(1):e61505. doi: 10.5812/traumamon.61505.

Published online 2018 July 23. **Research Article**

Effect of Modafinil Administration on the Level of Consciousness in Patients with Brain Injuries of Moderate Severity

Omid Moradi Moghadam [1], Nima Nematollahi [2], Ebadallah Shiri Malek Abad [3], Valiolah Hasani [2], Alireza Tabibkhooei [2], Mehrdad Sheikhvatan [2] and Mohammad Niakan Lahiji [1, *]

[1] Anesthesiology and Critical Care Department of Iran University Medical Sciences, Rasool-e-Akram Complex Hospital, Trauma and Injury Research Center, Iran University of Medical Sciences, Tehran, Iran
[2] Iran University of Medical Sciences, Tehran, Iran
[3] AJA University of Medical Sciences, Tehran, Iran

[*] *Corresponding author*: Anesthesiology and Critical Care Department of Iran University Medical Sciences, Rasool-e-Akram Complex Hospital, Trauma and Injury Research Center, Iran University of Medical Sciences, Tehran, Iran. E-mail: m.niakan48@gmail.com

Received 2017 September 09; **Revised** 2017 December 24; **Accepted** 2018 January 09.

Abstract

Background: With regards to the importance of traumatic brain injury (TBI) and its high incidence rate in Iran as well as its severe consequences, it is important to determine the safety and efficiency of modafinil to increase the level of consciousness in hospitalized TBI patients.

Methods: This double-blind randomized controlled trial was done during 2016. Sixty patients with TBI and moderate GCS score between 9 and 13 had the inclusion criteria and entered the study and were divided into two groups. Patients in the treatment group received 200 mg of modafinil once a day and the control group received the placebo. Overall, 24 hours after admission, defined as base day, modafinil was prescribed for 196 hours after admission and GCS scores were recorded: this period was defined as the last day. Level of consciousness in both treatment and control groups was assessed by the GCS score. Data were analyzed by SPSS version 21 software using the independent t-test with intention-to-treat approach.

Results: Among 60 patients, there were 34 (56.66%) males and 26 (43%) females; 45 (75%) survived. The ITT analysis was employed to assess changes in the level of consciousness (LOC) after prescribing modafinil and placebo. Based on the findings, modafinil prescription was not associated with significant differences in LoC in the first time period (24 hours after) and the last day (196 hours) ($P > 0.05$).

Conclusions: Prescribing modafinil was not associated with significant changes in LoC in comparison with the placebo.

Keywords: Modafinil, Level of Consciousness, Glasgow Coma Scale, Traumatic Brain Injury

1. Background

Traumatic brain injury (TBI) is a common problem (1). The world health organization report stated that the TBI burden will rise above other diseases by 2020, and will become a major cause of morbidity and mortality (2). Furthermore, TBI is a major cause of death in patients 45 years old and older; almost 40% of all deaths in the United States of America are attributed to TBI (3-5). It has been estimated that the annual cost of TBIs in the USA is about 56.2 billion dollars (6). Injuries that are related to road traffic accidents, falls, and violence are the most important causes of TBIs (6). Annual costs of TBIs in the US are about 56.3 billion dollars (7).

In Iran, TBIs are the second leading cause of death in different age groups, following cardiovascular diseases. After age adjustment, it is the first leading cause of death in under 40-year-olds. In Iran, each year about 27000 people die because of road traffic accidents (8). Furthermore, precise data on TBIs are not available in Iran, yet a recently conducted study on this issue has shown that most of the victims are young, with an average age of 34.7 years old; it was also revealed that TBIs account for 53.5% of deaths due to road traffic accidents. Most of them were head injuries and were hospitalized (9).

About two-thirds of TBI victims develop neurological complications, which can last for decades (10, 11). In addition, it causes behavioral and mood problems, memory impairment, and operational functions that are difficult to treat (12). Common symptoms are excessive daytime sleepiness and fatigue, which can significantly reduce the quality of life and daily operations, such as work and social activities (13). Different parameters are used in neu-

rological examination of TBI patients; one of them is the level of consciousness (LoC). The glasgow coma scale (GCS) has been widely accepted as the standard assessment instrument for TBI (14). The GCS is a scientific instrument for monitoring LoC changes based on the best physical, verbal, and visual responses. A low GCS status is an indicator of an increased risk of an intracranial lesion, and is an important factor indicating the necessity for surgery to remove the hematoma (15). Furthermore, GSC is the most important factor in prognosis and outcome of patients with TBIs. Also, professionals use the GCS before using CT-scan to determine, which patients require contrast studies to diagnose bleeding. It has been proven that there is a strong association between glasgow coma and risk of hematoma inside the skull (16, 17).

The prognosis can be determined based on the GCS. However, it has shortcomings, for instance, patients, who are in a coma have an endotracheal tube in their trachea that prevents verbal assessment. The FOUR criteria is a new scale that has been developed with GCS's shortcomings in mind and can be useful for ICU patients. This new scale contains novel neurological-clinical findings that are applicable in patients with consciousness disorders. The exact examination of the LoC is one of the main challenges of clinical care, and for this reason, having a scale to examine the LoC is crucial, so that the clinical team constantly monitors LoC changes. Based on what was mentioned before, an exact and applicable criterion, which can be used by physicians and nurses is needed. The FOUR criteria have advantages that can be used alongside the CGS (18, 19). Modafinil is a new awakening drug that is different from amphetamine and methylphenidate, and is also known as the classical psychic stimulus. Its exact mechanism is not yet known yet probably works through the effect on both the noradrenergic and dopaminergic systems and interaction with hypocretin/orexin, which induces awakening (20). Initially, it was approved by the food and drug administration for patients with extreme daytime sleepiness (EDS). In 5% of cases it causes anorexia and increased consciousness (21). Until now, various studies have been conducted on the use of this drug to treat EDS and LoC in patients with a diagnosis of HIV, lung cancer, stroke, primary biliary cirrhosis, and LoC due to TBIs (5, 22-25).

2. Objectives

The current study aimed at investigating the impact of modafinil on LoC in patients with TBIs of moderate severity, hospitalized at the intensive care unit (ICU) of the researcher's, during year 2016.

3. Methods

This double-blind randomized controlled clinical trial was done in 2016 on hospitalized ICU patients. The study population consisted of all volunteer TBI patients that had undergone surgery and were between 18 and 65 years old with normal GCS score (9 to 13) during the admission time. FOUR score was also assessed at the time of admission.

Patients with history of severe hypersensitivity to modafinil, angina pectoris, myocardial ischemia, left ventricular hypertrophy, and mitral valve prolapse, for whom Modafinil could have side effects (26, 27), were excluded.

Overall, 60 patients had the inclusion criteria and were entered in the study. Patients were randomized to two groups using a random numbers table, using their chart ID. Each group consisted of 30 patients.

To ensure the safety and efficiency of modafinil, 200 mg of modafinil was prescribed for the treatment group and the researchers assessed the initial outcomes in the first 24 hours after admission using the GCS score.

Patients in the treatment group received 200 mg of modafinil once a day and the control group received the placebo. Twenty-four hours after admission was defined as base day, and modafinil was prescribed 196 hours after admission and GCS scores were recorded, and this period was defined as the last day.

Ethical committee of the university approved the study and initial written consent was obtained from the patient's family at the randomization stage.

Level of consciousness in both treatment and control groups was assessed by the GCS score. Overall, 15 patients died at the end of the study period. Data were analyzed by SPSS version 21 using the independent t-test with intention-to-treat approach.

4. Results

Based on the findings of the current study, the patients were mostly male (56.66%), between 51 and 60 kg (50%), and 55% were in BMI category of 18.5 to 24.9. Furthermore, 75% were hospitalized because of traffic-accidents. Thirty-six patients had systolic blood pressure of 101 to 110. The average blood pressure in patients in the group of 81 to 90 (mm Hg) in 45 (75%) was the most frequent. Out of 60 participants, 45 (75%) survived (Table 1).

At time of admission, based on the findings, Mean FOUR score was 10.67. Its average in males and females was 10.54 and 10.89, respectively. The mean GCS score at the time of admission was 10.95 (Table 2).

Daily changes of level of consciousness according to GCS score in different time periods after prescribing modafinil showed that modafinil administration was not

Table 1. Demographic Characteristics of Patients

Variable	Frequency	Percentage (%)
Age (years old)		
18 - 40	15	25
41 - 50	40	66.66
51 - 65	5	3.34
Gender		
Male	34	56.66
Female	26	43.34
Weight (kg)		
Less than 50	3	5
51 to 65	30	50
66 to 80	12	20
More than 80	15	25
BMI		
18.5 to 24.9	33	55
25 to 29.9	12	20
30 to 34.9	12	20
35 and higher	3	5
Cause of injury		
Traffic accident	45	75
Fall	12	20
Others	3	About 5
Systolic blood pressure (mm HG)		
Less than 90	3	5
90 to 100	9	15
101 to 110	36	60
111 to 120	9	15
More than 120	3	5
MAP (mm HG)		
Less than 70	3	5
70 to 80	6	10
81 to 90	6	10
More than 90	6	10
Prognosis		
Survived	45	75
Death	15	25

Table 2. Level of Consciousness at the Admission Time

Indicator	Mean	SD	Median
FOUR			
Male	10.54	0.38	11
Female	10.89	0.2	11
Total	10.67	0.29	11
GCS			
Male	10.71	0.25	10
Female	11.9	0.41	10
Total	10.95	0.36	11

associated with significant differences at the base day (24 hours after admission/base) and the last day (196 hours after admission) ($P > 0.05$) (Table 3).

5. Discussion

Galvin and colleagues (2010) estimated that verbal score after prescribing modafinil and placebo was 3 ± 1.2 and 3.8 ± 2.5, respectively. By considering a 95% confidence interval and a power equal to 99%, sample size for each group in the current study was 30. Variables were as follows: gender, age, cause of injury, prognosis, systolic blood pressure, MAP, BMI, GCS, and FOUR score.

The current study used the intention-to-treat approach to examine daily changes of LoC after prescribing modafinil or placebo at different time periods. No significant differences were found between treatment and control groups in terms of LoC at the first time period (base) and the last day.

Jha and Colleagues (25) investigated the impact of modafinil on fatigue and sleepiness in patients with TBIs; 53 patients with TBIs randomly received 400 mg modafinil or equal amounts of placebo. Primary outcomes for fatigue measured the severity of fatigue and sleep. The findings showed that there was no statistical difference between modafinil and placebo in terms of durational effects and basic scores in fatigue severity at the fourth or tenth week. In terms of daily sleepiness, no significant change was observed between modafinil and placebo. In another study, Stankoff et al. (28) examined the impact of modafinil in patients with MS. They examined 115 patients, which were divided to two groups: 56 patients treated with modafinil and 56 with placebo. They found that there was no statistical difference between the two groups and no improvement in patients receiving modafinil (27). Kaiser and Colleagues also examined the impact of modafinil on sleepiness and fatigue. They divided 20 patients to two groups, intervention and control. Their study revealed a significant impact on severe fatigue in the intervention group, yet it did not have an impact on fatigue after the accident (5). Ondo et al. (29), in a study on patients with parkinson, found that modafinil had a significant impact on severe

Table 3. Level of Consciousness According to GCS Score at Base Day and Last Day

	Base Day (24 h After Admission)		Last Day (196 h After Admission)		Independent Samples T-Test	P Value
	Modafinil M(SD)	Placebo M(SD)	Modafinil M(SD)	Placebo M(SD)		
GCS score in patients with moderate coma	11.1 (0.23)	11.26 (0.48)	13 (0.18)	12.85 (0.56)	1.826	0.144

sleepiness. Different studies showed that modafinil had effects on fatigue, for instance, Rammohan et al. (30) showed that it had positive effects on patients with MS.

Furthermore, TBIs caused serious changes in the LoC and assessment was difficult. The ability to respond to internal and external stimuli was affected. Rezaee et al. found that the average score in the FOUR criteria before and after the intervention had a significant difference, yet no difference was found in GCS (31, 32). Some studies compared GCS and FOUR criteria system, and most of them mentioned the latter to be a better scale.

5.1. Conclusions

Findings of the current study showed that modafinil does not significantly affect LoC.

References

1. Zeiler KJ, Zeiler FA. Social Determinants of Traumatic Brain Injury in the North American Indigenous Population: A Review. *Can J Neurol Sci*. 2017;**44**(5):525–31. doi: 10.1017/cjn.2017.49. [PubMed: 28535822].
2. Boniface R, Lugazia ER, Ntungi AM, Kiloloma O. Management and outcome of traumatic brain injury patients at Muhimbili Orthopaedic Institute Dar es Salaam, Tanzania. *Pan Afr Med J*. 2017;**26**:140. doi: 10.11604/pamj.2017.26.140.10345. [PubMed: 28533863]. [PubMed Central: PMC5429442].
3. Swanson TM, Isaacson BM, Cyborski CM, French LM, Tsao JW, Pasquina PF. Traumatic Brain Injury Incidence, Clinical Overview, and Policies in the US Military Health System Since 2000. *Public Health Rep*. 2017;**132**(2):251–9. doi: 10.1177/0033354916687748. [PubMed: 28135424]. [PubMed Central: PMC5349478].
4. Bergersen K, Halvorsen JO, Tryti EA, Taylor SI, Olsen A. A systematic literature review of psychotherapeutic treatment of prolonged symptoms after mild traumatic brain injury. *Brain Inj*. 2017;**31**(3):279–89. doi: 10.1080/02699052.2016.1255779. [PubMed: 28125305].
5. Kaiser PR, Valko PO, Werth E, Thomann J, Meier J, Stocker R, et al. Modafinil ameliorates excessive daytime sleepiness after traumatic brain injury. *Neurology*. 2010;**75**(20):1780–5. doi: 10.1212/WNL.0b013e3181fd62a2. [PubMed: 21079179].
6. Crompton EM, Lubomirova I, Cotlarciuc I, Han TS, Sharma SD, Sharma P. Meta-Analysis of Therapeutic Hypothermia for Traumatic Brain Injury in Adult and Pediatric Patients. *Crit Care Med*. 2017;**45**(4):575–83. doi: 10.1097/CCM.0000000000002205. [PubMed: 27941370].
7. Dismuke CE, Walker RJ, Egede LE. Utilization and Cost of Health Services in Individuals With Traumatic Brain Injury. *Glob J Health Sci*. 2015;**7**(6):156–69. doi: 10.5539/gjhs.v7n6p156. [PubMed: 26153156]. [PubMed Central: PMC4803849].
8. Fakharian E, Mohammadzadeh M, Behdadmehr S, Sabri HR, Mirzadeh AS, Mohammadzadeh J. Repetitive Traumatic Brain Injury in Patients From Kashan, Iran. *Trauma Mon*. 2016;**21**(4). e23869. doi: 10.5812/traumamon.23869. [PubMed: 28180123]. [PubMed Central: PMC5282941].
9. Kavosi Z, Jafari A, Hatam N, Enaami M. The economic burden of traumatic brain injury due to fatal traffic accidents in shahid rajaei trauma hospital, shiraz, iran. *Arch Trauma Res*. 2015;**4**(1). e22594. doi: 10.5812/atr.22594. [PubMed: 25834791]. [PubMed Central: PMC4377539].
10. Koponen S, Taiminen T, Portin R, Himanen L, Isoniemi H, Heinonen H, et al. Axis I and II psychiatric disorders after traumatic brain injury: a 30-year follow-up study. *Am J Psychiatry*. 2002;**159**(8):1315–21. doi: 10.1176/appi.ajp.159.8.1315. [PubMed: 12153823].
11. Himanen L, Portin R, Isoniemi H, Helenius H, Kurki T, Tenovuo O. Longitudinal cognitive changes in traumatic brain injury: a 30-year follow-up study. *Neurology*. 2006;**66**(2):187–92. doi: 10.1212/01.wnl.0000194264.60150.d3. [PubMed: 16434651].
12. Lippert-Gruner M, Kuchta J, Hellmich M, Klug N. Neurobehavioural deficits after severe traumatic brain injury (TBI). *Brain Inj*. 2006;**20**(6):569–74. doi: 10.1080/02699050600664467. [PubMed: 16754282].
13. Baumann CR, Werth E, Stocker R, Ludwig S, Bassetti CL. Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. *Brain*. 2007;**130**(Pt 7):1873–83. doi: 10.1093/brain/awm109. [PubMed: 17584779].
14. Cheng K, Bassil R, Carandang R, Hall W, Muehlschlegel S. The Estimated Verbal GCS Subscore in Intubated Traumatic Brain Injury Patients: Is it Really Better? *J Neurotrauma*. 2017;**34**(8):1603–9. doi: 10.1089/neu.2016.4657. [PubMed: 27774844]. [PubMed Central: PMC5397225].
15. Kasprowicz M, Burzynska M, Melcer T, Kubler A. A comparison of the Full Outline of UnResponsiveness (FOUR) score and Glasgow Coma Score (GCS) in predictive modelling in traumatic brain injury. *Br J Neurosurg*. 2016;**30**(2):211–20. doi: 10.3109/02688697.2016.1161173. [PubMed: 27001246].
16. Kehoe A, Smith JE, Bouamra O, Edwards A, Yates D, Lecky F. Older patients with traumatic brain injury present with a higher GCS score than younger patients for a given severity of injury. *Emerg Med J*. 2016;**33**(6):381–5. doi: 10.1136/emermed-2015-205180. [PubMed: 26825613].
17. Ward Fuller G, Hernandez M, Pallot D, Lecky F, Stevenson M, Gabbe B. Health State Preference Weights for the Glasgow Outcome Scale Following Traumatic Brain Injury: A Systematic Review and Mapping Study. *Value Health*. 2017;**20**(1):141–51. doi: 10.1016/j.jval.2016.09.2398. [PubMed: 28212955]. [PubMed Central: PMC5339086].
18. Saika A, Bansal S, Philip M, Devi BI, Shukla DP. Prognostic value of FOUR and GCS scores in determining mortality in patients with traumatic brain injury. *Acta Neurochir (Wien)*. 2015;**157**(8):1323–8. doi: 10.1007/s00701-015-2469-6. [PubMed: 26077394].
19. McNett M, Amato S, Gianakis A, Grimm D, Philippbar SA, Belle J, et al. The FOUR score and GCS as predictors of outcome after traumatic brain injury. *Neurocrit Care*. 2014;**21**(1):52–7. doi: 10.1007/s12028-013-9947-6. [PubMed: 24408147].
20. Wisor JP, Eriksson KS. Dopaminergic-adrenergic interactions in the wake promoting mechanism of modafinil. *Neuroscience*. 2005;**132**(4):1027–34. doi: 10.1016/j.neuroscience.2005.02.003. [PubMed: 15857707].
21. Prasuna PL, Sudhakar TP. Impact of Modafinil Add-on with Atypical Anti-psychotics on Excessive Daytime Drowsiness. *Indian J Psychol Med*. 2015;**37**(4):388–92. doi: 10.4103/0253-7176.168561. [PubMed: 26702168]. [PubMed Central: PMC4676202].

22. Silveira MG, Gossard AA, Stahler AC, Jorgensen RA, Petz JL, Ali AH, et al. A Randomized, Placebo-Controlled Clinical Trial of Efficacy and Safety: Modafinil in the Treatment of Fatigue in Patients With Primary Biliary Cirrhosis. *Am J Ther*. 2017;**24**(2):e167–76. doi: 10.1097/MJT.0000000000000387. [PubMed: 27148676].
23. McElhiney M, Rabkin J, Van Gorp W, Rabkin R. Modafinil effects on cognitive function in HIV+ patients treated for fatigue: a placebo controlled study. *J Clin Exp Neuropsychol*. 2010;**32**(5):474–80. doi: 10.1080/13803390903201769. [PubMed: 19937504]. [PubMed Central: PMC2878385].
24. Spathis A, Fife K, Blackhall F, Dutton S, Bahadori R, Wharton R, et al. Modafinil for the treatment of fatigue in lung cancer: results of a placebo-controlled, double-blind, randomized trial. *J Clin Oncol*. 2014;**32**(18):1882–8. doi: 10.1200/JCO.2013.54.4346. [PubMed: 24778393].
25. Jha A, Weintraub A, Allshouse A, Morey C, Cusick C, Kittelson J, et al. A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. *J Head Trauma Rehabil*. 2008;**23**(1):52–63. doi: 10.1097/01.HTR.0000308721.77911.ea. [PubMed: 18219235].
26. Zukkoor S. *The Safety of Stimulant Medication Use in Cardiovascular and Arrhythmia Patients*. American College of Cardiology; 2015. Available from: http://www.acc.org/latest-in-cardiology/articles/2015/04/28/10/06/the-safety-of-stimulant-medication-use-in-cardiovascular-and-arrhythmia-patients.
27. [No Author Listed]. *Archiveid Drug Label,*. 2007. Available from: https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=4884.
28. Stankoff B, Waubant E, Confavreux C, Edan G, Debouverie M, Rumbach L, et al. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. *Neurology*. 2005;**64**(7):1139–43. doi: 10.1212/01.WNL.0000158272.27070.6A. [PubMed: 15824337].
29. Ondo WG, Fayle R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. *J Neurol Neurosurg Psychiatry*. 2005;**76**(12):1636–9. doi: 10.1136/jnnp.2005.065870. [PubMed: 16291885]. [PubMed Central: PMC1739456].
30. Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollak CP, Nagaraja HN. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *J Neurol Neurosurg Psychiatry*. 2002;**72**(2):179–83. [PubMed: 11796766]. [PubMed Central: PMC1737733].
31. Rezaee H, Jahani Y, Pakzad Moghaddam S, Monfared S, Ebrahimi Hooshyar A. Effect of Stimulation Program on Consciousness of Traumatic Brain Injury Patients: A Camparison of Four and Gcs Scale. *Iran J Anesth Critical Care*. 2015;**2**(2):98–104.
32. Sadaka F, Patel D, Lakshmanan R. The FOUR score predicts outcome in patients after traumatic brain injury. *Neurocrit Care*. 2012;**16**(1):95–101. doi: 10.1007/s12028-011-9617-5. [PubMed: 21845490].