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Research Article

The Effectiveness of Zolpidem in Improving Consciousness in Patients with Acute Brain Injury

*Alireza Rahat Dahmardeh[1], Masoum Khoshfetrat[2], Mehdi Heidari[1,3], Aliakbar Keykha[4,5]**

[1]*Department of Anesthesiology and Critical Care, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran.*

[2]*Department of Anesthesiology and Critical Care, Khatam-Al-Anbiya Hospital, Zahedan University of Medical Sciences, Zahedan, Iran.*

[3]*Clinical Immunology Research Center, Ali IbneAbitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran.*

[4]*Community Nursing Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.*

[5]*Department of Medical-Surgical Nursing, School of Nursing and Midwifery Zahedan University of Medical Sciences, Zahedan, Iran.*

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ABSTRACT

Background: Disorders of consciousness, including the vegetative state (VS) and the minimally conscious state (MCS) following brain damage and various complications for the patient, also have economic and social consequences. However, there is still no definitive or effective treatment for this condition. However, there is still no definitive or effective treatment for this condition. Therefore, this study aims to investigate the effectiveness of zolpidem in improving consciousness in patients with acute brain injury.

Methods: The present quasi-experimental study was performed from 2020 to 2021 after obtaining the necessary permissions from Zahedan University of Medical Sciences, Iran. Eighty patients with acute brain injury who met the study inclusion criteria were recruited and randomized into zolpidem and placebo groups. In the zolpidem group, 10 mg zolpidem tablets were gavage twice daily. In the placebo group, a placebo tablet with the same appearance as zolpidem was gavage twice daily for 14 days. The consciousness level of patients was measured daily until the outcome (ICU discharge or expiration) was established. Eventually, a comparative data analysis was conducted to determine zolpidem's efficacy in enhancing consciousness, reducing mechanical ventilation duration, and improving patient outcomes.

Results: The mean GCS score in the zolpidem group was 6.1±2.4 on admission and 11.6±3.8 at the end of the study, compared to 5.9±1.7 on admission and 11.3±2.8 at the end of the study, for the placebo group (p=0.154 and p=0.211, respectively). The mean duration of mechanical ventilation was 24.41±9.14 days in the zolpidem group and 23.16±10.72 days in the placebo group (P=0.529). Twenty-eight patients in the zolpidem group were discharged from ICU, and 12 expired. For the placebo group, 26 patients were discharged from ICU, while 14 were expired (p=0.87). No statistically significant difference was found in any of the measured variables between the two groups.

Conclusion: The results have shown that zolpidem administration had no statistically significant effect on improving the level of consciousness and reducing mechanical ventilation duration and clinical outcomes in acute brain injury patients.

The authors declare no conflicts of interest.

*Corresponding author.
E-mail address: aliakbar.keykha@gmail.com

Introduction

Improving the quality of care has increased the survivance of patients after brain injury [1]. These patients have long periods of unconsciousness or coma. Some patients may recover with appropriate treatment and care within days or weeks after the initial coma. But many of them find a slight increase in their level of consciousness and experience a vegetative state (VS) or minimally conscious state (MCS) [2]. Brain injuries that lead to VS or MCS are mostly untreatable and lead to permanent disability. The performed treatments do not significantly affect improving the patient's condition. But generally, the treatment of patients with VS and MCS focuses on pharmacological interventions, sensory stimulation, and cognitive rehabilitation protocols [3-4]. In the temporary deep brain stimulation (DBS) method, flexible electrode wires are implanted under stereotactic surgery with local anesthesia in different parts of the brain based on the type of brain damage of the patient, and the brain is stimulated with a low-intensity of electric current in short periods [5]. In some studies, electrical stimulation of the mesencephalic reticular formation and the centromedian–parafascicularis nucleus complex has partially improved consciousness in patients with VS [6]. But this treatment method is very complicated, requiring advanced equipment, a well-equipped intensive care unit, and skilled staff, and in addition to not being widely available, it also causes many side effects such as bleeding and brain infection for patients [7]. For this reason, medicinal methods that increase a patient's consciousness have gained more acceptance. Because in addition to being able to use them more widely to increase patient consciousness. They also have fewer side effects [8]. Pharmacological agents may effectively arouse patients with impaired consciousness through cortical pathways and neurotransmitter changes. The results have shown that after prescribing drugs that affect the central nervous system, such as bromocriptine [3], zolpidem, amantadine, and apomorphine, positive changes occur in the nervous condition of patients and sometimes lead to significant improvement. However, more studies are needed to understand the mechanism of these drugs in increasing consciousness and to determine which drug can provide a better neurological outcome [9-10]. Zolpidem is a selective GABA-w1 receptor agonist. These receptors regulate the sleep-wake cycle and reduce the restlessness of patients with consciousness disorders. Recent studies have shown that zolpidem can increase consciousness in VS patients by binding to the GABA-w1 receptor. Also, It may reduce metabolic disturbance and abnormal metabolism of damaged brain cells by improving perfusion in the damaged area [11-12]. Of course, zolpidem's effects in improving neural flexibility are short-term, and long-term effects have not been observed so far [13] in a systematic review study that examined the effect of zolpidem on the level of consciousness. It was stated that administering zolpidem is not beneficial in all patients with consciousness disorders. In patients with anoxic cerebral encephalopathy and traumatic brain injuries, no improvement in brain function has been observed following zolpidem administration. Available evidence has only shown the positive effects of zolpidem on improving brain function in patients whose brainstem was not damaged. Therefore, more studies are required to prove the positive effects of zolpidem in improving patients' consciousness [14]. Therefore, this study was conducted to investigate the effectiveness of zolpidem in improving consciousness in patients with acute brain injury.

Methods

After obtaining the necessary permissions and the ethical code of IR.ZAUMS.REC.1397.369 from Zahedan University of Medical Sciences, the present quasi-experimental study was performed in its affiliated hospitals between 2020 to 2021. Following previous studies [15] and based on the formulation for the sample size calculation, the sample size of 80 was estimated, considering a type-I error of 0.05 and a power of 80 percent. Based on the study inclusion criteria, 80 patients with acute impaired consciousness levels were recruited using the convenience sampling method immediately after admission to the intensive care unit (ICU). The patients were randomly assigned into two zolpidem and placebo groups, each of 40 patients. For randomization, according to the sample size, 80 cards with red and blue colors were prepared and placed inside a dark box. One card was taken from the box after including the first patient in the study. The patient would be assigned to the zolpidem group if the card were red. Otherwise, the patient was assigned to the placebo group. With the continuation of sampling, the taking of cards continued until 40 patients were assigned to each of the two groups.

The study's inclusion criteria were patients with acute brain injury who were between 15 and 75 years old and had Glasgow Coma Scale (GCS) $\leq$ 8 with stable hemodynamics.

The exclusion criteria included a history of insomnia and taking zolpidem, a history of convulsions and taking anticonvulsant drugs, developing symptoms of allergy to zolpidem after starting the treatment, performing surgery during the zolpidem treatment period, and the patient dying before completing the study period.

After allocating the patients to two groups, their initial consciousness level and demographic information were recorded. The zolpidem group received a 10 mg zolpidem tablet twice daily for 14 days (manufactured by Sobhan Pharmaceutical Co., Iran). Placebo tablets are identical to zolpidem tablets in shape and size and were given by

gavage to the placebo group twice daily for 14 days. One researcher prepared the solutions for gavage by dissolving either zolpidem or a placebo. Prepared solutions were administered to the patients via gavage by an anesthesiology resident blinded to the drug type and grouping. The consciousness level of the patients was also measured daily by the same anesthesiology resident. For patients who needed sedation, 25 to 50 mcg/h fentanyl infusion was used, and two hours after the cessation of sedation, the patient's consciousness level was measured. On day 14, the zolpidem and placebo administration was terminated. However, the evaluation of patients continued until their end outcome was established (recovery and ICU discharge or death). Finally, data were analyzed to discern the effect of zolpidem on the patients' consciousness level and outcomes.

Statistical analysis

Collected data were analyzed using SPSS software version 27. Patients' demographic variables were compared using descriptive statistics (frequency, mean, and standard deviation). Since checking data normality using the Kolmogorov-Smirnov test yielded insignificant results, parametric statistical tests were chosen for data comparison. An independent statistical t-test was applied to compare the two groups regarding mean age, consciousness level scores, mechanical ventilation duration, and length of ICU stay. The gender and outcome comparison of the patients was performed using Chi-square. A one-way ANOVA test was used to compare scores of consciousness level based on the cause of brain damage.

Ethical considerations

Before entering the study, the first-degree family members of all patients had been given detailed explanations regarding the study objectives and information confidentiality. Additionally, they were asked to sign informed written consent forms if willing to involve their patients in the study. The data collection form was designed not to include first and last names in the demographic information section to ensure anonymity. The research plan of this article was approved by the ethics committee of Zahedan University of Medical Sciences under the ethical code of IR.ZAUMS.REC.1397.369. During the study, official correspondence and necessary coordination were established with hospital administrators. All permissions received from the Deputy of Research at Zahedan University were shared with the hospital officials and patients' families to assure them of the procedure's legitimacy and validity.

Results

Of the total of 80 patients examined, 56 (70%) patients suffered an acute brain injury and reduced consciousness level due to brain trauma, 18 (22.5%) due to cerebral ischemia, and 6 (7. 5%) due to cerebral hemorrhage. The zolpidem group included 27 (67.5%) patients with brain trauma, 9 (22.5%) with cerebral ischemia, and 4 (10%) with cerebral hemorrhage. In comparison, the placebo group had 29 (72.5%) patients with brain trauma, 9 (22.5%) with cerebral ischemia, and 2 (5%) with cerebral hemorrhage. A comparison of patients regarding the cause of acute brain injury revealed no statistically significant difference between the two groups (p=0.298). The mean age of patients was 37.7±16.3 years. 55 (68.8%) patients were male, and 25 (31.3%) were female. The mean age of patients was 36.7±16.5 years in the zolpidem group compared to 38.16±6.2 years in the placebo group (p=0.596). There were 26 (65%) men and 14 (35%) women in the zolpidem group and 29 (72. 5%) men and 11 (27.5%) women in the placebo group (p=0.496). No significant difference was noticed between the two groups regarding age and gender.

The mean GCS score in the zolpidem group was 6.1±2.4 on admission and 11.6±3.8 at the end of the study. The same score was obtained as 5.9±1.7 and 11.3±2.8 on admission and end of the study in the placebo group. The difference between patients' admission and final GCS scores was 5.7±3.7 in the zolpidem group and 5.2±2.8 in the placebo group. The two groups had no significant difference in any of the cases (Table 1).

Table 1- A comparison of the mean and standard deviation of admission and final GCS scores of patients between the two groups.

Variable	Group Zolpidem	Placebo	P value
Mean GCS score on admission	6.1±2.4	5.9±1.7	0.134
Mean final GCS score	11.6±3.8	11.3±2.8	0.311
The mean difference between admission and final GCS scores	5.7±3.7	5.2±2.8	0.279

The mean difference of GCS score in traumatic, ischemic, and hemorrhagic patients was 6.2±3.9, 5.7±2.1, and 6.5±1.3, respectively, in the zolpidem group and 6.2±1.4, 5.1±1.7 and 6.4±2.1, respectively, in the placebo group. One-way ANOVA test (p=0.494, p=0.221, and p=0.071, respectively) showed no significant difference between the groups regarding changes in the level of consciousness during the zolpidem treatment period.

The mean duration of mechanical ventilation was 24.41±9.14 days in the zolpidem group and 23.16±10.72 days in the placebo group. The independent t-test displayed no statistically significant difference in ventilation duration between the two groups (p=0.529). The mean duration of hospitalization was 36.55±14.28 and 31.86±16.49 days in the zolpidem and placebo groups, respectively. Based on the independent t-test results, no significant difference was observed between the two groups regarding the hospital stay duration

(p=0.223). Of 40 patients in the zolpidem group, 28 were discharged from ICU, and 12 were expired. The number of discharged and expired patients in the placebo group was 26 and 14, respectively. The chi-square results established no statistically significant difference between the two groups' final clinical outcomes of acute brain injury patients (p=0.87). The mean GCS score on admission was 8.84±2.03 in discharged patients and 6.11±1.08 in expired patients. Given the t-test results, the difference in GCS scores between discharged and expired patients was statistically insignificant (p=0.421).

Discussion

The study showed that zolpidem administration does not affect consciousness improvement, mechanical ventilation duration reduction, and outcomes of patients with acute brain injury. In agreement with the results of the present study, in a case report that prescribed zolpidem for one week to improve the brain function of a patient with a minimally conscious state due to traumatic brain injury, it was reported that after the administration of zolpidem, the patient's brain function not an improvement, instead, in some cases, the brain functional status of the patient worsened [16]. In a systematic review that examined 67 articles in which zolpidem was used to treat disorders of consciousness, movement, and other brain injuries such as dementia and encephalopathy, it was reported that zolpidem transiently reduced a wide range of neurodegenerative diseases. It treats movement and consciousness disorders. However most results were from case reports and small clinical trials, and only 11 studies had a sample size of more than 10 people. Therefore, although there is significant preliminary evidence of the transient effects of zolpidem in the treatment of various non-insomnia neurological disorders, due to the low reliability of the results, more research is needed to investigate the mechanisms and clarify the safety and effectiveness of this drug [17]. It appears that insomnia drugs can improve arousal and motor coordination.

Zolpidem is an imidazopyridine that is unique in its pharmacological action compared to other classes of sedative-hypnotics, such as benzodiazepines, antihistamines, or barbiturates. This uniqueness is due to the selective agonism of this drug on the ω1 receptor subtype of the γ-aminobutyric acid A (GABAA) receptor complex [18-19]. Specific brain regions are rich in these receptors, including the basal ganglia and striatum output structures to the thalamus and motor cortices. This may explain some of the remarkable and paradoxical effects observed. Therefore, this unique action of zolpidem may be a potential therapeutic mechanism to restore brain function in patients with various neurological disorders [17]. GABA inhibitors drugs can control the high levels of glutamate, which cause excessive stimulation of brain receptors and induce a cascade of stimulatory mechanisms leading to apoptosis of brain cells due to intracellular invasion of calcium [20-21]. However all these issues are mostly theoretical, and we currently do not have a demonstrable clinical effect for the effect of this drug in improving patients' consciousness [17]. In line with the results of the present study, in a clinical trial study, 84 patients with disorders of consciousness (DOCs) were treated with 10 mg zolpidem daily for 4 months. The results showed that only the consciousness level of 4 of them improved temporarily. Therefore, it was concluded that these small changes could not be attributed to the effects of zolpidem; it is better to conduct more studies to prove the effects and to know the mechanism of this drug in increasing the consciousness of patients [22]. In another clinical trial, eight patients with the persistent vegetative state (PVS) 1 to 114 months after brain injury and eight healthy subjects were first treated with a placebo, then zolpidem was administered, and 30 minutes after drug administration as baseline record changes were considered. The results showed that in all subjects, only minor clinical changes, such as yawning and hiccups, increased cerebral cortex activity in the EEG, along with increased heart rate without an increase in sympathetic tone were created [23]. Thonnard et al. evaluated sixty patients with traumatic brain injury with a vegetative state (unresponsive wakefulness syndrome) (n=28) and minimally conscious state (n=32) before and one hour after the administration of 10 mg zolpidem using a coma recovery scale-revised (CRS-R). The results showed that, in general, the behavioral performance scores of the patients decreased after zolpidem administration. Only twelve patients (20%) showed behavioral improvement (increased CRS-R score) after zolpidem administration and could obey orders. A minimally conscious patient also significantly improved behavior after receiving zolpidem. In this patient, a double-blind, placebo-controlled trial was conducted to characterize the effects of zolpidem better, but the patient did not show any clinical improvement in this trial. Therefore, it was concluded that zolpidem does not cause significant clinical changes in improving chronic consciousness disorders in patients [24]. Although the method of evaluating patients, the sample size, and the time of examining patients in the studies mentioned above differed from the present study, the results obtained in all studies show that zolpidem does not significantly increase the consciousness of patients with brain damage.

Conclusion

Zolpidem administration does not significantly affect consciousness improvement, mechanical ventilation duration reduction, and outcomes in acute brain injury patients. Thus, the regular application of this drug in the ICU setting to enhance the consciousness level of patients

is not recommended. Further clinical trials with large sample sizes are suggested to verify the positive effects of this drug.

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Author contributions

Alireza Rahat Dahmardeh: Developing the research proposal, supervising the study, collecting data, and revising the manuscript.

Masoum Khoshfetrat: Developing the research proposal, executing the research, and collecting data.

Mehdi Heidari: Collaboration in research proposal and data collection.

Aliakbar Keykha: Collaboration in research proposal, data analysis, manuscript drafting, and final manuscript revising.

References

[1] Khalili H, Rakhsha A, Ghaedian T, Niakan A, Masoudi N. Application of brain perfusion SPECT in the evaluation of response to zolpidem therapy in consciousness disorder due to traumatic brain injury. Indian J Nucl Med. 2020; 35(4):315-20.

[2] Whyte J, Myers R. Incidence of clinically significant responses to zolpidem among patients with disorders of consciousness: a preliminary placebo controlled trial. Am J Phys Med Rehabil. 2009; 88(5):410-8.

[3] Passler MA, Riggs RV. Positive outcomes in traumatic brain injury-vegetative state: patients treated with bromocriptine. Arch Phys Med Rehabil. 2001; 82(3):311-5.

[4] Giacino JT, Zasler ND. Outcome after severe traumatic brain injury: coma, the vegetative state, and the minimally responsive state. The Journal of Head Trauma Rehabilitation. 1995;10(1):41-56

[5] Yamamoto T, Katayama Y, Kano T, Kobayashi K, Oshima H, Fukaya C. Deep brain stimulation for the treatment of parkinsonian, essential, and poststroke tremor: a suitable stimulation method and changes in effective stimulation intensity. J Neurosurg. 2004;101(2):201-9.

[6] Yamamoto T, Katayama Y, Kobayashi K, Oshima H, Fukaya C, Tsubokawa T. Deep brain stimulation for the treatment of vegetative state. Eur J Neurosci. 2010; 32(7):1145-51.

[7] Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, et al. Deep brain stimulation: current challenges and future directions. Nat Rev Neurol. 2019; 15(3):148-60.

[8] Ciurleo R, Bramanti P, Calabrò RS. Pharmacotherapy for Disorders of Consciousness: Are 'Awakening' Drugs Really a Possibility? Drugs. 2013; 73(17):1849-62.

[9] Gosseries O, Charland-Verville V, Thonnard M, Bodart O, Laureys S, Demertzi A. Amantadine, apomorphine and zolpidem in the treatment of disorders of consciousness. Curr Pharm Des. 2014; 20(26):4167-84.

[10] Cohen SI, Duong TT. Increased arousal in a patient with anoxic brain injury after administration of zolpidem. Am J Phys Med Rehabil. 2008; 87(3):229-31.

[11] Pistoia F, Mura E, Govoni S, Fini M, Sarà M. Awakenings and Awareness Recovery in Disorders of Consciousness. CNS Drugs. 2010; 24(8):625-38.

[12] Hall SD, Yamawaki N, Fisher AE, Clauss RP, Woodhall GL, Stanford IM. GABA (A) alpha-1 subunit mediated desynchronization of elevated low frequency oscillations alleviates specific dysfunction in stroke–a case report. Clinical Neurophysiology. 2010; 121(4):549-55.

[13] Sanna E, Busonero F, Talani G, Carta M, Massa F, Peis M, et al. Comparison of the effects of zaleplon, zolpidem, and triazolam at various GABAA receptor subtypes. Eur J Pharmacol. 2002; 451(2):103-10.

[14] Noormandi A, Shahrokhi M, Khalili H. Potential benefits of zolpidem in disorders of consciousness. Expert Rev Clin Pharmacol. 2017;10(9):983-92.

[15] Bruno M-A, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J Neurol. 2011; 258(7):1373-84.

[16] Singh R, McDonald C, Dawson K, Lewis S, Pringle A-M, Smith S, et al. Zolpidem in a minimally conscious state. Brain Injury. 2008; 22(1):103-6.

[17] Bomalaski MN, Claflin ES, Townsend W, Peterson MD. Zolpidem for the Treatment of Neurologic Disorders: A Systematic Review. JAMA Neurol. 2017; 74(9):1130-9.

[18] Dixon CL, Harrison NL, Lynch JW, Keramidas A. Zolpidem and eszopiclone prime α1β2γ2 GABAA receptors for longer duration of activity. Br J Pharmacol. 2015; 172(14):3522-36.

[19] Salvà P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic implications. Clin Pharmacokinet. 1995; 29(3):142-

53.
[20] Clauss RP. Neurotransmitters in Coma, Vegetative and Minimally Conscious States, pharmacological interventions. Med Hypotheses. 2010;75(3):287-90.
[21] Clauss RP. Neurotransmitters in disorders of consciousness and brain damage. Medical Hypotheses. 2011; 77(2):209-13.
[22] Whyte J, Rajan R, Rosenbaum A, Katz D, Kalmar K, Seel R, et al. Zolpidem and restoration of consciousness. Am J Phys Med Rehabil. 2014; 93(2):101-13.
[23] Machado C, Estévez M, Rodríguez R, Pérez-Nellar J, Chinchilla M, DeFina P, et al. Zolpidem arousing effect in persistent vegetative state patients: autonomic, EEG and behavioral assessment. Curr Pharm Des. 2014; 20(26):4185-202.
[24] Thonnard M, Gosseries O, Demertzi A, Lugo Z, Vanhaudenhuyse A, Bruno MA, et al. Effect of zolpidem in chronic disorders of consciousness: a prospective open-label study. Funct Neurol. 2013; 28(4):259-64.