Application of Brain Perfusion SPECT in the Evaluation of Response to Zolpidem Therapy in Consciousness Disorder Due to Traumatic Brain Injury

Abstract

Background: Traumatic brain injury (TBI) is a critical health problem with various comorbidities and socioeconomic consequences. Tending to increase in recent decades, TBI results in more cases of consciousness disorders including vegetative state (VS)/minimally conscious state (MCS). However, no definite or effective treatment still exists for these conditions. The aim of this article is to study the effects of zolpidem in patients with VS caused by TBI by using brain perfusion single-photon emission computed tomography (SPECT). Materials and Methods: This was a prospective clinical trial on a cohort of patients with VS. We evaluated the TBI database to find VS/MCS patients, between the ages of 20 and 65 years. We received written consent from their family members prior to enrollment and compared their clinical status and brain perfusion SPECT prior and after weeks of zolpidem therapy. Results: Among the 12 patients included in this study, six patients changed to MCS after 2 weeks. Comparison of their motor score, revealed a statistically significant difference (2.08 vs. 3.75, P = 0.007, respectively). None of the quantitative or qualitative brain perfusion parameters showed any differences after zolpidem therapy. However, the perfusion pattern, with focal or multifocal cortical defects, was significantly more prevalent in the responder group (five patients vs. one patient, P = 0.015). Conclusion: Zolpidem therapy may improve consciousness levels and motor function in a considerable portion of VS patients with TBI. This study showed that the presence of focal brain perfusion defect can predict response to zolpidem.

Keywords: Brain perfusion single-photon emission computed tomography, consciousness disorders, traumatic brain injury, zolpidem

Introduction

Traumatic brain injury (TBI) is a prevailing critical health problem worldwide. TBI occurs when an external force is transmitted to the head, resulting in neurological and cognitive damage.[1] During recent decades, there have been many growing incidences of TBI around the world. In addition, improvement of emergency care is leading to higher rates of trauma survivors, with more patients with TBI suffering from consciousness disorders.[2]

Disorders of consciousness, such as vegetative state (VS) and minimally conscious state (MCS), are associated with significant morbidity and adverse complications.[3] Unfortunately, there are no clinically efficient therapies available for these conditions. Nonetheless, several medical and surgical interventions have been introduced for these patients with variable response rates and controversial efficacy.[4] Zolpidem, a gamma-aminobutyric acid (GABA)-ergic sedative drug, has been used in some clinical report trials and is proposed to improve arousal in consciousness disorders.[5] Since 2000 when Clauss et al. reported an awakening response in a case of VS after incidental administration of zolpidem, other investigators have also reported similar cases.[6-8] These findings have paved the way for the development of new clinical trial initiatives. In 2009, in a prospective, placebo-controlled trial, Whyte et al. reported that only one out of 18 patients responded positively to zolpidem[9] and Thonnard et al.[10] could not find any significant clinical response in sixty patients with consciousness disorders. However, after a thorough study of 167 patients with consciousness disorders,

How to cite this article: 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;35:315-20.
Du et al. suggested a statistically significant improvement in brain perfusion of patients with nonbrainstem injuries.[11] Most of these improved findings were diminished after zolpidem discontinuation, and there was no significant overall prognosis improvement.

Brain perfusion single-photon emission computed tomography (SPECT) specifies and shows relative regional cerebral perfusion. Several studies have concluded that patients with consciousness disorders show improved regional cerebral perfusion after zolpidem administration.[8,12,13] This effect appears several months after the injury, which is within a reasonable timeline.[5]

In this study, we aimed to evaluate the efficacy of zolpidem in patients with brain damage after trauma using brain perfusion SPECT along with clinical assessment.

Materials and Methods

This is a prospective clinical trial study approved by the local ethical committee and registered in the national clinical trial registry. All patients were carefully selected and enrolled from the TBI database of a tertiary trauma center. The inclusion criteria were as follows: (1) being in a VS after TBI for 6–24 months; (2) having a medically stable condition; (3) not having severe complications or other comorbidities in addition to brain damage; (4) age range of 20–65 years; and (5) written consent from the patient’s family members or guardian to participate in the study. Patients were excluded if (1) any evidence of allergic reaction to zolpidem was identified, (2) additional surgical or medical intervention during zolpidem treatment was indicated, and (3) in case of poor-quality SPECT images, patients were excluded. Then, the motor score of extremities, based on the motor part of Glasgow Coma Scale (GCS), was evaluated immediately before baseline brain perfusion SPECT with 99mTc-ethylcysteinate dimer (ECD). After brain SPECT, each patient was prescribed 10 mg of zolpidem, to be taken twice orally, per day. A tablet of 10 mg zolpidem was dissolved in a 250 cc in a cup of water and administered via the patient’s gastrostomy for each dose. After 2 weeks, consciousness state, motor score evaluation, and brain perfusion SPECT responses were assessed for reaction to the oral administration of 10 mg zolpidem. Patients with changes in consciousness state from VS to MCS (defined as any meaningful response to environmental stimuli which cannot be considered as reflexive activity) were defined as responders.

Clinical evaluation

After consent from family members or guardians was obtained, each patient was clinically evaluated by a neurosurgeon in the outpatient department clinic before starting zolpidem therapy and was re-evaluated, by the same physician, 1 h after zolpidem administration. The surgeon assessed the consciousness status and GCS motor response of each patient. Afterward, the best motor score was evaluated in response to painful stimulant for all the four extremities based on six motor score parts of GCS consisting of: (1) no contraction, (2) extension, (3) abnormal flexion, (4) normal flexion, (5) localized, and (6) response to command.

Brain perfusion single-photon emission computed tomography

Patients remained in a quiet room with dim lighting for 10 min after intravenous (IV) catheter insertion. Then, 45 min after IV injection of 20 mCi 99mTc-ECD, SPECT imaging was performed by a dual-head gamma camera with 360° arch including 120 projections (30 s/projection). The projections were reconstructed by Ordered subset expectation maximization (OSEM) (order: 4; subset: 10; postfilter: Butterworth; cutoff frequency: 0.5, order: 10) with application of Chang’s attenuation correction. The reconstructed data were evaluated by a nuclear medicine specialist using the NeuroGam software (Rev. 0 Copyright© 2004 by GE Medical Systems). For visual comparison between the two scans for each patient, the nuclear medicine specialist was blinded to scan date and compared a set of two scans for each patient. The scan results were visually interpreted and categorized as positive change (if the postzolpidem scan showed better perfusion compared to prezolpidem scan), negative change (if there was worsening of perfusion), and no change. The quantitative data were represented as the mean percentage of counts in each brain lobe compared to the maximum cerebral count. The estimation of three-dimensional cortical region of interests for different brain lobes is shown in Figure 1.

Statistical analysis

The results of clinical and imaging data before and 2 weeks after administration of zolpidem were statistically analyzed with the (SPSS for Windows, Version 16.0. Chicago, SPSS Inc). For comparison of quantitative parameters (motor score and regional cerebral perfusion percentages) before and after the study, Wilcoxon test was used. For comparison of qualitative and quantitative parameters between two groups of responders and nonresponders, Chi-square and Mann–Whitney U-tests were applied. Statistical significance was identified as P < 0.05.

Results

After our inclusion/exclusion criteria, 12 patients from the total pool of 52 patients in VS (10 male) were eligible. The mean age of the selected patients was 36 years, with a mean disease duration of 13 months. Patients’ demographic data, brain perfusion findings, pre- and post-zolpidem motor score, as well as response status of each patient are illustrated in Table 1.

Comparison of motor score before and after zolpidem therapy revealed a statistically significant
improvement \((P = 0.007)\). However, there is no significant difference between quantitative regional cerebral perfusion data before and after zolpidem therapy [Table 2]. In addition, visual comparison of brain perfusion SPECT scans by a nuclear medicine specialist failed to find any patient with significant change after zolpidem therapy.

Then, the patients were categorized as responders and nonresponders on the basis of a positive change in consciousness status (change from VS to MCS or higher). In comparison of responders and nonresponders, no statistically significant difference was found according to age \((P = 0.937)\), disease duration \((P = 0.485)\), and baseline motor score \((P = 0.589)\). However, when we categorized patients based on their baseline brain perfusion, scan findings for those with focal discrete cortical defects and those without cortical defect (homogenous cortical perfusion), and compared the number of each pattern

![Figure 1: Estimation of three-dimensional cortical region of interests for different brain lobes in NeuroGam software](image)

| Patient | Age  | Sex  | Duration (months) | Motor score 1 | Motor score 2 | Scan pattern                                      | Response |
|---------|------|------|-------------------|---------------|---------------|---------------------------------------------------|----------|
| AA      | 30   | Male | 15                | Upper extremities: 2 Lower extremities: 2 | Homogenous perfusion | No |
| FF      | 26   | Female | 11                | Upper extremities: 3 Lower extremities: 2 | Homogenous perfusion | No |
| AM      | 50   | Male | 13                | Upper extremities: 3 Lower extremities: 3 | Homogenous perfusion | No |
| AR      | 45   | Male | 15                | Upper extremities: 3 Lower extremities: 3 | Homogenous perfusion | No |
| EB      | 21   | Male | 11                | Upper extremities: 1 Lower extremities: 2 | Global decreased perfusion | No |
| AV      | 45   | Male | 16                | Upper extremities: 2 Lower extremities: 2 | Homogenous perfusion | No |
| AJ      | 20   | Male | 10                | Upper extremities: 2 Lower extremities: 3 | Focal perfusion defect in the right frontal lobe | Yes |
| KR      | 45   | Male | 8                 | Upper extremities: 2 Lower extremities: 5 | Homogenous perfusion | Yes |
| MK      | 20   | Male | 14                | Upper extremities: 2 Lower extremities: 3 | Focal perfusion defect in the right frontal and parietal lobes | Yes |
| PS      | 52   | Female | 18                | Upper extremities: 1 Lower extremities: 4 | Focal perfusion defect in the right parietal lobe | Yes |
| NS      | 64   | Male | 10                | Upper extremities: 4 Lower extremities: 5 | Focal perfusion defect in the right frontal and parietal lobes | Yes |
| MP      | 23   | Male | 15                | Upper extremities: 5 Lower extremities: 5 | Focal perfusion defect in the left parietal lobe | Yes |

Table 1: Patients’ demographic data, brain perfusion findings, pre- and post-zolpidem motor score, as well as response (change from VS to minimally conscious state or higher level of consciousness) status
between responder and nonresponder groups, a statistically significant difference was found \((P = 0.015)\) [Table 3].

There were five patients with focal cortical perfusion defect and one patient without cortical defect in the responder group, whereas all nonresponder patients had no evidence of discrete cortical perfusion defect. The dominant location of cortical perfusion defect in those five patients was frontal or parietal lobe. Brain perfusion SPECT images of two patients with and without focal cortical perfusion defect are depicted in Figure 2.

**Discussion**

This study revealed that zolpidem administration may improve motor score in VS patients due to trauma (50%). There are some case reports indicative of zolpidem efficacy in these patients, with limited number of clinical trials investigating this effect in larger samples. Furthermore, our study revealed a potential role for brain perfusion SPECT in a more efficient selection of patients for zolpidem therapy.

Whyte et al. studied the clinical effect of zolpidem in 15 patients with consciousness disorder, applying Comma Recovery Score-Revised (CRS-R) before and after zolpidem administration. They found no significant improvement, with just one patient changed from VS to MCS.\[9\] Another clinical trial by Thonnard et al. on sixty patients also showed no statistically significant change 1 h after the administration of zolpidem in consciousness disorder patients, although CRS-R increased in 12 patients.\[10\] Compared to other clinical studies, our study revealed higher clinical response rates after zolpidem therapy. This difference may partly contribute to the difference in the baseline features of patients. While there are various etiologies with wider range of disease duration reported in some studies, we aimed to select a more homogenous sample of patients with TBI and disease duration of 6–24 months. On the other hand, we used higher daily dose of zolpidem (10 mg twice daily) for 2 weeks, whereas the majority of previous trials evaluated lower doses. Calabrò et al. reported a case of VS patient who responded to zolpidem only after administration of 20 mg zolpidem, with stronger response after higher dose of 30 mg, indicating some degree of dose–response relation.\[14\] Increased frequency of zolpidem administration for 2 weeks, further explains the higher response rate in our study.

In addition, varying definitions of response with different scaling methods, add some complexity when comparing the results from each study. While we utilized a sensitive scale for the evaluation of consciousness (presence of any positive reaction to vocal stimulants) and motor score, which are the most widely used criteria in the clinical evaluation of patients with TBI, previous studies used other scoring systems such as CRS-R. Applying different criteria in a study by Whyte et al. in 84 patients, they defined 28 (38%) patients as probable responder with only four patients finally diagnosed as definite responders.\[15\]

We also obtained brain perfusion SPECT before and after zolpidem administration for better evaluation of response mechanisms. Although we found no significant change in

### Table 2: Comparison of regional cerebral perfusion in terms of mean percent activity as compared to maximum cerebral count according to eight brain lobes before and 2 weeks after zolpidem therapy

| Location                  | Prezolpidem Mean±SD | Postzolpidem Mean±SD | \(P^a\) |
|---------------------------|---------------------|----------------------|--------|
| Left frontal lobe         | 67.9±3.7            | 66.7±5.0             | 0.239  |
| Right frontal lobe        | 65.8±8.0            | 65.1±6.8             | 0.695  |
| Left occipital lobe       | 69.8±6.4            | 69.9±7.3             | 0.814  |
| Right occipital lobe      | 66.6±8.3            | 67.3±7.3             | 0.610  |
| Left parietal lobe        | 64.2±6.6            | 65.1±10.4            | 0.530  |
| Right parietal lobe       | 62.9±10.7           | 64.9±9.3             | 0.158  |
| Left temporal lobe        | 63.6±7.6            | 62.9±7.5             | 0.480  |
| Right temporal lobe       | 60.9±8.8            | 61.2±8.0             | 0.754  |

\(P^a<0.05\) is significant. SD: Standard deviation

### Table 3: Comparison of patients’ baseline characteristics between responders and nonresponders

|                          | Responders | Nonresponders | \(P^a\) |
|--------------------------|------------|---------------|--------|
| Age (years)              | 37.6       | 36.1          | 0.937  |
| Disease duration (months) | 12.5       | 13.5          | 0.485  |
| Baseline motor score (mean) | 2.5       | 2.3           | 0.589  |
| Presence of focal cortical defect (%) | 5         | 0             | 0.015  |

\(P^a<0.05\) is significant

---

![Figure 2](image-url)
Our results also show that patients with perfusion defects in brain injury (4 MCS and 19 conscious patients) were evaluated by brain perfusion SPECT before and after 2 weeks of zolpidem administration. Ten patients showed evidence of improved cerebral perfusion after zolpidem, and the authors found more clinical improvement of these patients after 4 months as compared to those with no significant change in brain perfusion. Although several case reports also indicated positive brain perfusion changes in those unconscious patients with considerable clinical response after zolpidem administration, it should be acknowledged that there are also some reported cases with clinical improvement without evidence of brain perfusion changes. Based on our findings, and the evidence from the literature, we suggest that positive perfusion changes are not essential for indicating clinical improvement, although in patients with stronger responses, as reported in some cases, it may have a role in the pathophysiology of zolpidem therapy in consciousness disorders.

We also compared some baseline features of patients between responder and nonresponder groups. Among the variables of age, sex, baseline motor score, and brain perfusion pattern, the presence of focal cortical perfusion defect was the only parameter that was significantly different between the two groups. In the study by Whyte et al. in 2014, none of the baseline demographic variables including age, duration, and etiology of consciousness disorder were associated with a response to zolpidem. Hiu et al. found that enhancing GABA signaling during repair phase in mice with induced stroke (4 weeks after stroke) can improve recovery and suggested the potential role of this signaling as a therapeutic target, where zolpidem can act as a GABAergic agent. They emphasized the importance of time interval from stroke needed for the efficacy of zolpidem because in early weeks after stroke, zolpidem has no effect on patients’ recovery. Thus, patients with disease duration of < 4 months are unlikely to respond to zolpidem compared to those with more than 4 months’ disease duration. Studying 165 patients with brain perfusion SPECT, Du et al. also suggested that regional cerebral perfusion was significantly improved in patients with nonbrainstem lesion (cortical lesions), whereas patients with brainstem lesion showed no significant change in brain perfusion SPECT before and after 1 week of zolpidem therapy. The authors stated that the severity and location of brain lesions are related to zolpidem response and explained that zolpidem, acting as a GABAergic agonist, reversed the brain dormancy. Hence, the clinical response will be more prominent in case the dormant brain area involves a critical functional region. Our results also show that patients with perfusion defects in brain cortex are more likely to respond to zolpidem. Additionally, patients with a culprit lesion not located in the cortex, may have other mechanism for consciousness disorders which are not related to GABAergic system. However, considering the small sample size in our study, further research is needed to investigate the role of brain perfusion studies with SPECT or especially F18-fluorodeoxyglucose positron emission tomography in the prediction of zolpidem response in larger population of TBI patients.

**Conclusion**

This study showed that the presence of focal brain perfusion defect in brain perfusion SPECT imaging can predict response to zolpidem therapy in VS patients with TBI. Although more dedicated studies with larger sample size is needed in this regard.

**Acknowledgment**

The present article was extracted from a thesis written by Abbas Rakhsha and was financially supported by Shiraz University of Medical Sciences, Shiraz, Iran (grant no. 15648). The authors would like to thank the staff of the nuclear medicine department of Namazi Hospital for their cooperation and the Center for Development of Clinical Research of Namazi Hospital for their contribution to the statistical analysis.

**Financial support and sponsorship**

This study was financially supported by Shiraz University of Medical Sciences, Shiraz, Iran (grant no. 15648).

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. McKee AC, Daneshvar DH. The Neuropathology of Traumatic Brain Injury. Handbook of Clinical Neurology. Vol. 127. Amsterdam, Netherlands: Elsevier B.V., 2015. p. 45-66.
2. Aisiku IP, Silvestri DM, Robertson CS. Critical care management of traumatic brain injury. In: Winn HR, editor. Youmans and Winn Neurological Surgery E-Book. Vol. 4. New York, USA: Elsevier Health Sciences; 2016. p. 2876-7.
3. Hirschberg R, Giacino JT. The vegetative and minimally conscious states: Diagnosis, prognosis and treatment. Neurol Clin 2011;29:773-86.
4. Georgiopoulou M, Katsakiori P, Kefalopoulou Z, Ellul J, Chroni E, Constantyannis C. Vegetative state and minimally conscious state: A review of the therapeutic interventions. Stereotact Funct Neurosurg 2010;88:199-207.
5. Sutton JA, Claus RP. A review of the evidence of zolpidem efficacy in neurological disability after brain damage due to stroke, trauma and hypoxia: A justification of further clinical trials. Brain Inj 2017;31:1019-27.
6. Claus RP, Güldenpfennig WM, Nel HW, Sathekge MM, Venkannagari RR. Extraordinary arousal from semi-comatose state on zolpidem: A case report. S Afr Med J 2000;90:68-72.
7. Claus RP, van der Merwe CE, Nel HW. Arousal from a semi-comatose state on zolpidem. S Afr Med J 2001;91:788-9.
8. Clauss RP, Nel WH. Effect of zolpidem on brain injury and diachisis as detected by 99mTc HMPAO brain SPECT in humans. Arzneimittelforschung 2004;54:641-6.
9. 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;88:410-8.
10. Thonnard M, Gossierco O, Demertzi A, Lugo Z, Vanhauwenbuye A, Bruno MA, et al. Effect of zolpidem in chronic disorders of consciousness: A prospective open-label study. Funct Neurol 2013;28:259-64.
11. Du B, Shan A, Zhang Y, Zhong X, Chen D, Cai K. Zolpidem arouses patients in vegetative state after brain injury: Quantitative evaluation and indications. Am J Med Sci 2014;347:178-82.
12. Nyakale N, Clauss R, Nel H, Sathekge M. Clinical and brain SPECT changes in stroke patients on zolpidem therapy. Funct Neurol Rehabil Ergon 2011;1:435.
13. Nyakale NE, Clauss RP, Nel W, Sathekge M. Clinical and brain SPECT scan response to zolpidem in patients after brain damage. Arzneimittelforschung 2010;60:177-81.
14. Calabrò RS, Aricò I, De Salvo S, Conti-Nibali V, Bramanti P. Transient awakening from vegetative state: Is high-dose zolpidem more effective? Psychiatry Clin Neurosci 2015;69:122-3.
15. 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;93:101-13.
16. Hiu T, Farzampour Z, Paz JT, Wang EH, Badgely C, Olson A, et al. Enhanced phasic GABA inhibition during the repair phase of stroke: A novel therapeutic target. Brain 2016;139:468-80.