

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 2 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, 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 conscious disorders,

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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 ^{99m}Tc-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 gastrotomy 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 ^{99m}T-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

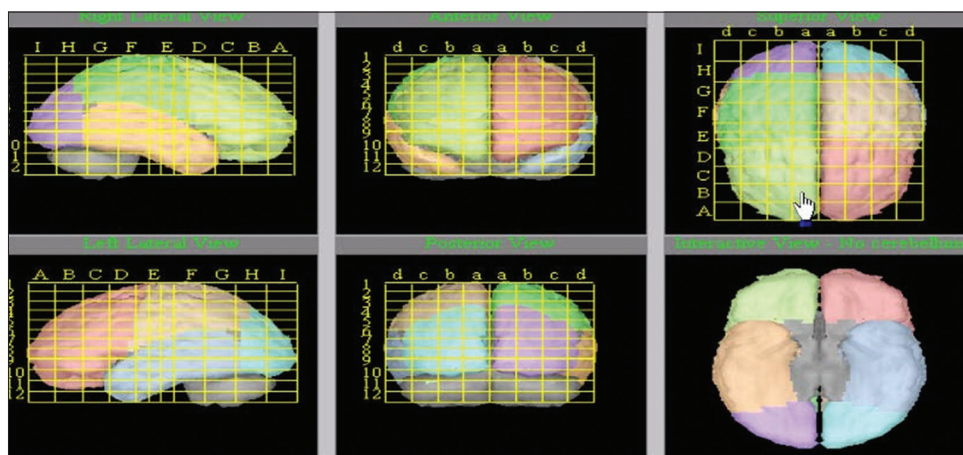


Figure 1: Estimation of three-dimensional cortical region of interests for different brain lobes in NeuroGam software

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

Patient	Age	Sex	Duration (months)	Motor score 1	Motor score 2	Scan pattern	Response
AA	30	Male	15	Upper extremities: 2 Lower extremities: 2	Upper extremities: 2 Lower extremities: 2	Homogenous perfusion	No
FF	26	Female	11	Upper extremities: 3 Lower extremities: 3	Upper extremities: 3 Lower extremities: 3	Homogenous perfusion	No
AM	50	Male	13	Upper extremities: 3 Lower extremities: 0	Upper extremities: 3 Lower extremities: 0	Homogenous perfusion	No
AR	45	Male	15	Upper extremities: 3 Lower extremities: 3	Upper extremities: 4 Lower extremities: 3	Homogenous perfusion	No
EB	21	Male	11	Upper extremities: 1 Lower extremities: 2	Upper extremities: 2 Lower extremities: 2	Global decreased perfusion	No
AV	45	Male	16	Upper extremities: 2 Lower extremities: 2	Upper extremities: 3 Lower extremities: 3	Homogenous perfusion	No
AJ	20	Male	10	Upper extremities: 2 Lower extremities: 2	Upper extremities: 4 Lower extremities: 5	Focal perfusion defect in the right frontal lobe	Yes
KR	45	Male	8	Upper extremities: 2 Lower extremities: 3	Upper extremities: 5 Lower extremities: 5	Homogenous perfusion	Yes
MK	20	Male	14	Upper extremities: 2 Lower extremities: 2	Upper extremities: 3 Lower extremities: 3	Focal perfusion defect in the right frontal and parietal lobes	Yes
PS	52	Female	18	Upper extremities: 1 Lower extremities: 1	Upper extremities: 3 Lower extremities: 4	Focal perfusion defect in the right parietal lobe	Yes
NS	64	Male	10	Upper extremities: 4 Lower extremities: 4	Upper extremities: 5 Lower extremities: 5	Focal perfusion defect in the right frontal and parietal lobes	Yes
MP	23	Male	15	Upper extremities: 2 Lower extremities: 2	Upper extremities: 5 Lower extremities: 4	Focal perfusion defect in the left parietal lobe	Yes

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	Mean±SD		P ^a
	Prezolpidem	Postzolpidem	
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	64.4±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

^a $P < 0.05$ 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

^a $P < 0.05$ is significant

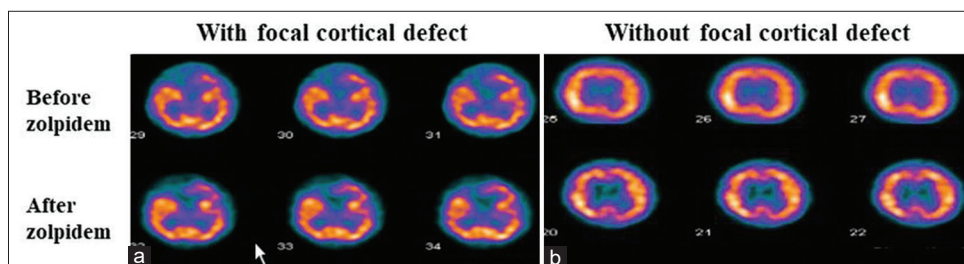


Figure 2: Transaxial slices of brain perfusion single-photon emission computed tomography in a responder patient (a) with focal cortical defect and (b) in a nonresponder patient without cortical defect. There is no significant change in relative brain perfusion before and after zolpidem therapy in both patients

regional cerebral perfusion after zolpidem administration, our results suggest a possible role for the presence of focal cortical perfusion defect as a predictor of response to zolpidem. In a study by Nyakale *et al.*, 23 patients with brain injury (4 MCS and 19 conscious patients) were evaluated by brain perfusion SPECT before and after 2 weeks of zolpidem administration.^[13] 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.^[13] Although several case reports also indicated positive brain perfusion changes in those unconscious patients with considerable clinical response after zolpidem administration,^[8] it should be acknowledged that there are also some reported cases with clinical improvement without evidence of brain perfusion changes.^[12] 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.^[15] 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 GABA-ergic 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.^[16] Thus, patients with disease duration of < 4 months are unlikely to respond to zolpidem compared to those with more than 4 months' disease duration.^[5] 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.^[11] 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.^[11] 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.

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Conflicts of interest

There are no conflicts of interest.

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