Original article

Evaluation of hyperbaric oxygen treatment of neuropsychiatric disorders following traumatic brain injury

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Keywords: *traumatic brain injury; hyperbaric oxygenation; computed tomography, single photon; emission computed tomography*

Background Improvement of clinical symptoms following hyperbaric oxygen (HBO) treatment of neuropsychiatric disorders arising from traumatic brain injury was proved by our previous study. This study was aim to obtain the evidence of other changes.

Methods Three hundred and ten patients with neuropsychiatric disorders arising from traumatic brain injury were treated twice with hyperbaric oxygen. Cerebral single photon emissions computed tomography (SPECT) images and computed tomography scans (CT) before and after hyperbaric oxygen treatment, were compared.

Results Before treatment, the proportion of abnormal cerebral changes detected by SPECT was 81.3% but only 15.2% by CT. After HBO treatment, 70.3% of SPECT scans showed no abnormalities and these patients were clinically improved. Treatment improved regional cerebral blood flow.

Conclusion SPECT was much more sensitive than CT in the diagnosis of neuropsychiatric disorders following hyperbaric oxygen treatment of neuropsychiatric disorders arising from traumatic brain injury.

Chin Med J 2006;119 (23):1978-1982

Psychiatric disorder often occurs after traumatic brain injury (TBI).[1] We noted the clinical effectiveness of hyperbaric oxygen (HBO) in treatment of neuropsychiatric disorders after TBI. Initially, the evaluation of its effects was only based on the improvement of clinical symptoms and there was no any other objective evidence to support the improvement. To study the effects of HBO on cerebral blood flow (CBF) and the usefulness of single photon emission computed tomography (SPECT) images in the diagnosis and assessment of neuropsychiatric disorders after TBI, we compared the results of cerebral SPECT and cerebral computed tomography (CT) before and after HBO treatment.

METHODS

Patients

Three hundred and ten patients with neuropsychiatric disorders arising from TBI were included (male 206, female 104, aged 12 to 78 years, mean 45 years). Eighteen patients were younger than 15 years, 20 patients were older than 60 years. All the patients had been diagnosed as head trauma based on (1) clear cut head trauma history; (2) headache, dizziness, poor memory, epilepsy, hysteria, poor concentration and attention deficit; (3) no history of intracranial space occupying lesion, hypertension or cardiovascular diseases. Among the 310 patients, 212 had a disease course of 1 to 6 months, 79 had a course of 6 months to 1 year and 19 had a course longer than 1 year. Two hundred and twenty-five patients had headache, dizziness, poor memory, epilepsy, hysteria and poor concentration. Forty-seven patients had epilepsy and thirty-eight patients had post traumatic hydrocephalus.

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^{99m}Tc-ECD SPECT imaging

^{99m}Tc-ECD brain SPECT was performed under resting condition. Each patient was injected with 740-925 MBq (20-25 mCi) of ^{99m}Tc-ECD. SPECT images were obtained at about 20 minutes to 1 hour after injection using a single head, rotating camera (Elscint APEX 609 RG; Elscint 1 td, Israel) and double head, rotating camera (Siemens ECAM deut, Germany) equipped with a low energy, high resolution collimator. Patients remained supine with eyes open in a softly light room. All patients were cooperative during the study. Data were collected from 60 projections in the 140 keV photopeak (15% window) over 360 degrees in a 64×64 matrix (Elscint APEX 609 RG) and 128×128 matrix (Siemens ECAM deut) with an acquisition time of 25-30 s/view. The total acquisition time was approximately 30 minutes (Elscint APEX 609 RG) and 15 minutes (Siemens ECAM deut). A zoom factor of 2 was used. Image reconstruction and analysis were performed using the computer system with filter back project (Elscint APEX 609 RG) and iterative back projection (Siemens ECAM deut), reconstruction and attenuation correction. The acquisition data were corrected for nonuniformity. Orthogonal transverse, coronal and sagittal images were generated, followed by orbitomeatal line (OML) reorientation of the reconstructed volume. The final data for visual interpretation consisted of 2-pixel thick OML level, transverse, coronal and sagittal slices. Images were made between 1 to 3 days before and after treatment. The same instrument was used before and after HBO treatment for examination of each patient and the images were collected and processed under the same conditions.

Semiquantitative analysis

To accurately evaluate rCBF, ^{99m}Tc-ECD uptake index was calculated for all patients. The uptake index was based on the ratio of ^{99m}Tc-ECD uptake in each of 24 regions of cerebral cortex to the area of cerebellum and four OML level slices (approximately OM, OM + 1.8 cm, OM + 3.6 cm, and OM + 5.4 cm) were selected. In these slices, operator defined (4×4 pixel) regions of interest (ROI) were drawn on some areas of left/right hemisphere. Using the system's ROI program, the same ROI could be easily moved to other area including cerebellum. The indices were recalculated from counts per pixel of the individual ROI for semiquantitative analysis.

^{99m}Tc-ECD-uptake index

The uptake index was (average ROI counts/pixel in the area of cerebral cortex)/(average ROI counts/pixel in the area of cerebellum). ^{99m}Tc-ECD-uptake index <0.9 was positive.[2]

Brain CT scan

Siemen Somoton DR3 type CT instrument (Germany) was used with scanning conditions: speed of 5 s/scan, 125 kV and 350 mAs. The thickness of every slice was 8 mm and table feed was 8-10 mm. Siemen Volume Zoom type CT instrument (Germany) was used under the scanning mode of 4 mm×5 mm with scanning conditions: speed of 1 s/scan, 120 kV, 300 mAs and table feed 20 mm. Siemen Samatom Sensation 16 type CT instrument (Germany) was used under the scanning mode of 4 mm×4.5 mm with scanning condition: speed of 1 s/scan, 120 kV, 300 mAs and table feed 18 mm. The scan plane was parallel to the orbitomeatal line. Patients were scanned by the same CT instrument for examination before and after HBO treatment and all images collected by the three CT instruments manipulated by H30 normal image manipulation software.

HBO therapy

Inside the NG 90 pure oxygen cabin, individual patients were treated under a pressure of 0.1 Mpa, inspired oxygen of 96% for 90 minutes daily for 20 days (2 courses).

Evaluation

The obtaining time of SPECT and CT images of each patient was within 1-3 days before and after HBO treatment. Two experienced nuclear medicine physicians, independently of CT data, together analysed SPECT images. Each CT image was analysed, similarly independent, by two experienced radiologists. Each image evaluation was: (1) cure: CT or SPECT showed the disappearance of foci; (2) improvement: CT or SPECT image showed that the foci were reduced by more than 1/3 in size; (3) inefficacy: CT or SPECT image showed foci were reduced by less than 1/3 or no change in size.

Statistical analysis

Statistical analysis was performed by cross table Chi-square test and statistical significance was defined as $P<0.05$. The analysis was performed using SPSS 10.0.

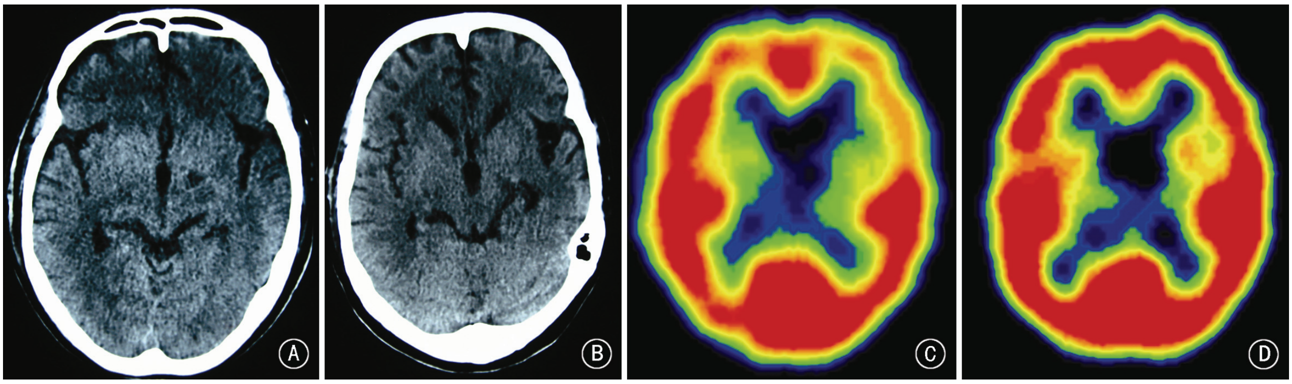

Fig. One typical case of a 41-year-old male patient suffered from brain trauma for 40 days induced by a traffic accident. He was conscious, dizzy, dysphoric, and poor in orientation. After treated with HBO for two courses, the patient recovered well. **A**: Before HBO treatment, CT showed ill defined and flaky focal with low density in both sides of frontal lobe. **B**: After treated with HBO for two courses, CT showed ill defined and flaky focal with low density in both sides of frontal lobe. **C**: Before HBO treatment, SPECT showed massive radioactive rarefaction in the left frontal lobe and local rarefaction in the right indicating that rCBF reduced. **D**: After treatment with HBO for two courses, SPECT showed radioactive distribution normal indicating that rCBF returned to normal.

RESULTS

Three hundred and ten patients with neuropsychiatric disorders after TBI were examined by cerebral SPECT before HBO treatment. Uptake index was positive in 252 (81.3%) patients and negative in 58 (18.7%) patients. Among the 252 patients, 168 had heterogeneous distribution of radioactivity with multiple small areas of lower radioactivity. Seventy-nine patients had 1 or 2 isolated small areas of lower radioactivity; 5 patients had multiple small areas of lower radioactivity and areas of abnormally high radioactivity. All patients were examined by brain CT before HBO treatment, 47 (15.2%) patients whose SPECT images were positive showed positive results. There was a significant difference in the positive rate between SPECT images and CT scan before HBO therapy (χ^2=620, P<0.01).

After two courses of HBO treatment, 252 previously positive patients were examined again by SPECT. The results revealed that 92 patients still had abnormal scans but 160 were now normal. The symptoms of headache, dizziness and poor concentration disappeared and of poor memory greatly improved in those patients whose SPECT had changed to normal. In 92 patients with positive SPECT, lower CBF area was decreased by 2/3 in 56 patients, decreased by 1/3 in 25 patients and reduced by less than 1/3 or no change in 11 patients — an overall improvement rate of 95.6%. Clinical symptoms were improved at the same time. After two courses of HBO treatment, 47 previously positive patients had a second CT. The results showed that 7 patients were now (CT) normal, 22 patients had smaller softening areas, 18 patients had no change — the overall improvement rate was 61.7%. In the 7 patients whose CT became normal, the SPECT still demonstrated varying degrees of low CBF. A typical case shows that lower radioactivity areas were decreased with treatment (Fig.). There was a significant difference in the positive rate between SPECT images and CT scans after HBO treatment (χ^2=299, P<0.01).

DISCUSSION

The diagnosis of neuropsychiatric disorders after TBI consists of physical examination, EEG, CT and MRI. But many patients can be misdiagnosed by physical examination alone. SPECT images can demonstrate abnormal regional CBF (rCBF) and therefore provide an objective basis for clinical diagnosis and evaluation.[2-4]

The main disadvantage of SPECT images is limited specificity. Many diseases of nervous system may result in abnormal rCBF and metabolism. Most patients with brain trauma did not have previous cerebral images, so we cannot estimate the false positive rate of cerebral SPECT images. However, with strict criteria of patient selection, excluding patients with other diseases of the nervous system, the false positive rate could be reduced.

Gowda et al[5] reported that CT findings were abnormal in 34% and SPECT in 63% in initial diagnostic evaluation of patients with mild traumatic brain injury. In this study, with neuropsychiatric disorders after TBI, 81.3% patients had abnormal SPECT images but only 15.2% had abnormal CT scans. SPECT detected more neurological damages and CT less than the initial diagnostic evaluation of patients with mild traumatic brain injury. After two courses of HBO, 47 patients had a second CT, 7 of them suggested no damage. However, these 7 patients still had clinical symptoms, and their SPECT images confirmed the existence of lower radioactive areas. Hofman et al[6] reported that there was a weak correlation between neuroimaging findings and neurocognitive outcomes.

Our high proportion of lower rCBF images of patients with neuropsychiatric disorders after TBI implies that a neuropsychiatric disorder after TBI is closely correlated with rCBF. Brain injury may result in persistent reductions in CBF in both the clinical[7-9] and experimental settings.[10] In and around traumatic contusions, cerebral blood flow is often near or below the threshold for ischemia. Baseline CBF and CBV increased significantly with increasing distance from the core of the lesion.[11] A reduced CBF in patients has been consistently associated with unfavorable neurological outcomes[12] and has been implicated in rendering the brain vulnerable to secondary damage.[13,14] Hattori et al[15] used positron emission tomography to assess CBF of patients with TBI and found that regional, contusional and pericontusional areas showed significantly lower CBF compared with normal volunteers. These results indicated that the basis of neuropsychiatric disorders after TBI was abnormal rCBF in affected areas of brain and the change of rCBF was closely correlated with the occurrence of clinical symptoms and prognosis.

The symptoms such as headache, dizziness, poor memory and poor concentration after TBI could be a result of ischemia and hypoxia caused by prolonged or recurrent cerebral vasospasm and local CBF decreases after brain trauma or chronic hydrocephalus. HBO treatment was found to inhibit neuronal death, improve blood flow in regions affected by chronic neurological disease as well as aerobic metabolism in brain injury, enhance neuronal viability by increasing the amount of dissolved oxygen in the blood without significantly changing blood viscosity, increase arterial oxygen pressure and content, improve and regulate cerebral metabolism,[16] allow collateral circulation to develop and accelerate the resolution of clinical symptoms.[17] HBO treatment can reduce cerebral vascular spasms, cerebral ischemia and hypoxia[18] and improve tissue oxygen delivery[19] especially to areas of diminished flow. One study suggests that HBO can cause a significant increase in brain oxygen tension to (151 ± 65) mmHg at 0.19 MPa and to (294 ± 134) mmHg at 0.28 MPa.[20] Besides, some studies have confirmed that there were viable but inactive nerve cells after TBI[21] and HBO can activate these nerve cells and reduce atrophy and apoptosis with regain of function.[22] The results of our study showed the distinctive beneficial effect of HBO in neuropsychiatric disorders after TBI and that SPECT images were far superior to CT scan in evaluating the effect of HBO and neuropsychiatric disorders after TBI.

REFERENCES

1. Deb S, Lyons I, Koutzoukis C, Ali I, McCarthy G. Rate of psychiatric illness 1 year after traumatic brain injury. Am J Psychiatry 1999; 156: 374-378.
2. Sun D. Radionuclide brain imaging. Hangzhou: The Publishing Company of Hangzhou University; 1997: 239-249.
3. Stamatakis EA, Wilson JT, Hadley DM, Wyper DJ. SPECT imaging in head injury interpreted with statistical parametric mapping. J Nucl Med 2002; 43: 476-483.
4. Van Laere K, Dumont F, Koole M, Dierckx R. Non-invasive methods for absolute cerebral blood flow measurement using ^{99m}Tc-ECD: a study in healthy volunteers. Eur J Nucl Med 2001; 28: 862-872.
5. Gowda NK, Agrawal D, Bal C, Chandrashekar N, Tripati M, Bandopadhyaya GP, et al. Technetium Tc-99m ethyl cysteinate dimer brain single-photon emission CT in mild traumatic brain injury: a prospective study. Am J Neuroradiol 2006; 27: 447-451.
6. Hofman PA, Stapert SZ, van Kroonenburgh MJ, Jolles J, de Kruijk J, Wilmink JT. MR imaging, single-photon emission CT, and neurocognitive performance after mild

traumatic brain injury. Am J Neuroradiol 2001; 22: 441-449.
7. Inoue Y, Shiozaki T, Tasaki O, Hayakata T, Ikegawa H, Yoshiya K, et al. Changes in cerebral blood flow from the acute to the chronic phase of severe head injury. J Neurotrauma 2005; 22: 1411-1418.
8. Oertel M, Boscardin WJ, Obrist WD, Glenn TC, McArthur DL, Gravori T,et al. Posttraumatic vasospasm: the epidemiology, severity, and time course of an underestimated phenomenon: a prospective study performed in 299 patients. J Neurosurg 2005; 103: 812-824.
9. Chieregato A, Fainardi E, Servadei F, Tanfani A, Pugliese G, Pascarella R, et al. Centrifugal distribution of regional cerebral blood flow and its time course in traumatic intracerebral haematomas. J Neurotrauma 2004; 21: 655-666.
10. Kochanek PM, Hendrich KS, Dixon CE, Schiding JK, Williams DS, Ho C. Cerebral blood flow at one year after controlled cortical impact in rats: assessment by magnetic resonance imaging. J Neurotrauma 2002; 19: 1029-1037.
11. Steiner LA, Coles JP, Johnston AJ, Czosnyka M, Fryer TD, Smielewski P, et al. Responses of posttraumatic pericontusional cerebral blood flow and blood volume to an increase in cerebral perfusion pressure. J Cereb Blood Flow Metab 2003; 23: 1371-1377.
12. Robertson CS, Contant CF, Gokaslan ZL, Narayan RK, Grossman RG. Cerebral blood flow, arteriovenous oxygen difference, and outcome in head injured patients. J Neurol Neurosurg Psychiatry 1992; 55: 594-603.
13. Hlatky R, Furuya Y, Valadka AB, Gonzalez J, Chacko A, Mizutani Y, et al. Dynamic autoregulatory response after severe head injury. J Neurosurg 2002; 97: 1054-1061.
14. Giri BK, Krishnappa IK, Bryan RM Jr, Robertson C, Watson J. Regional cerebral blood flow after cortical impact injury complicated by a secondary insult in rats. Stroke 2000; 31: 961-967.
15. Hattori N, Huang SC, Wu HM, Liao W, Glenn TC, Vespa PM, et al. PET investigation of post-traumatic cerebral blood volume and blood flow. Acta Neurochir Suppl 2003; 86: 49-52.
16. Badr AE, Yin W, Mychaskiw G, Zhang JH. Effect of hyperbaric oxygen on striatal metabolites: a microdialysis study in awake freely moving rats after MCA occlusion. Brain Res 2001; 916: 85-90.
17. Al Waili NS, Butler GJ, Beale J, Abdullah MS, Hamilton RW, Lee BY, et al. Hyperbaric oxygen in the treatment of patients with cerebral stroke, brain trauma, and neurologic disease. Adv Ther 2005; 22: 659-678.
18. Ren H, Wang W, Ge Z, Zhang J. Clinical, brain electric earth map, endothelin and transcranial ultrasonic Doppler findings after hyperbaric oxygen treatment for severe brain injury. Chin Med J 2001; 114: 387-390.
19. Sunami K, Takeda Y, Hashimoto M, Hirakawa M. Hyperbaric oxygen reduces infarct volume in rats by increasing oxygen supply to the ischemia periphery. Crit Care Med 2000; 28: 2831-2836.
20. Van Hulst RA, Haitsma JJ, Klein J, Lachmann B. Oxygen tension under hyperbaric conditions in healthy pig brain. Clin Physiol Funct Imaging 2003; 23: 143-148.
21. Chirumamilla S, Sun D, Bullock MR, Colello RJ. Traumatic brain injury induced cell proliferation in the adult mammalian central nervous system. J Neurotrauma 2002; 19: 693-703.
22. Calvert JW, Yin W, Patel M, Badr A, Mychaskiw G, Parent AD, et al. Hyperbaric oxygenation prevented brain injury induced by hypoxia- ischemia in a neonatal rat model. Brain Res 2002; 951: 1-8.

(Received February 8, 2006)
Edited by CHEN Li-min and SHEN Xi-bin