Effects of Normobaric Hyperoxia in Severe Acute Stroke: a Randomized Controlled Clinical Trial Study

Mehrdokht Mazdeh[1], Abbas Taher[2], Saadat Torabian[3], and Soroush Seifirad[4]

[1] *Department of Neurology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran*

[2] *Department of Anesthesiology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran*

[3] *Department of Public Health, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran*

[4] *Department of Pediatric Cardiology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*

Received: 30 Dec. 2013; Received in revised form: 10 Nov. 2014; Accepted: 22 Dec. 2014

Abstract- Oxygen therapy might increase damaged tissue oxygenation, turn on the aerobic pathway, and save neurons from death and could improve clinical outcome of the patients with stroke and head trauma. Hyperbaric oxygen therapy is accompanied by some unfavorable effects. Results of normobaric oxygen therapy on clinical outcomes of patients with stroke were controversial up till now. This study was therefore designed to evaluate effects of normobaric hyperoxia on clinical outcomes of patients with severe acute stroke. A total of 52 consecutive patients with stroke who meet the inclusion criteria of the study were entered into this randomized controlled clinical trial. The patients in the case group underwent oxygen therapy with Venturi mask for first 12 hours of admission. The patients were examined for neurologic defects at the time of discharge and after six months using both Barthel and modified Rankin Scale (mRS) neurologic disability scoring systems. There was no significant sex difference between the two groups (P=0.5). There was no statistically significant difference between ischemic-hemorrhagic stroke constitutions of two groups (P=0.2). There were no significant difference in Barthel index scores of both groups at the time of discharge as well as the follow-up examination (P=0.7) According to the mRS scoring system, there was no difference between the patients of both groups at the time of admission (P= 0.8), however after treatment there was a significant difference between mRS scores of the treated group compared to the controls (P=0.04). According to the results of this study, normobaric oxygen therapy in the first 12 hours of accident could improve long time outcome of the patients with either ischemic or hemorrhagic stroke.

Acta Med Iran 2015;53(11):676-680.

Keywords: Oxygen; Therapy; Cerebrovascular accident; Management

Introduction

More than two million annual hospitalizations due to brain damage are reported in Europe (1).

Neuroprotective interventions including intracranial pressure (ICP) and cerebral artery filling pressure (CPP) management as well as oxygen therapy improved clinical outcomes of patients with stroke and head trauma (2,3). Since we could not replace damaged neurons at this time, specific care of neurons of penumbra is critical and could improve clinical outcome of the patients with brain injury. Without sufficient interventions, neurons of penumbra become ischemic and efface the damaged area gradually (4). History of hyperbaric oxygen therapy in clinical and experimental studies on brain injury comes back to 1970s (5). In recent years, normobaric hyperoxia has been suggested and eliminated adverse effects of hyperbaric chambers (6,7).

An increased metabolism of neurons has been shown after brain injury (4). Because of increased rate of ions transportation after neuron injury, there is an increased need for glucose which is usually financed through glycogenolysis in astrocytes (8). On the other hand, tissue hypoxia after trauma shifts the glucose metabolism to the anaerobic pathway. Anaerobic metabolism of glucose produces lactate which is useless in damaged mitochondria of injured neurons (9-11). Hence, oxygen therapy might increase damaged tissue oxygenation, turn on the aerobic pathway, and save

Corresponding Author: S. Seifirad
Department of Pediatric Cardiology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 935 5799979, Fax: +98 21 66581594, E-mail address: sseifirad@gmail.com

neurons from death (12-14).

Beneficial effects of hyperbaric and normobaric oxygen therapy in traumatic patients is approved in the literature. In addition, hyperbaric oxygen therapy is accepted as a beneficial intervention in stroke, although it is accompanied by a number of adverse effects. To the best of our knowledge, application of normobaric oxygen in stroke is controversial up till now. This study was therefore conducted to evaluate effects of normobaric hyperoxia on clinical outcomes of patients with severe acute stroke.

Materials and Methods

A total of 52 consecutive patients with stroke who meet the inclusion criteria were entered into this randomized controlled clinical trial. The patients were selected from patients referred to the department of neurology in Farshchian hospital, an affiliated hospital of Hamadan university of medical sciences.

There was no difference in the medical management of the patients which randomly allocated into two groups except for oxygen therapy with Venturi mask for the first 12 hours of admission in the case group. The patients were admitted to the intensive care unit (ICU) and monitored carefully by expert nurses. Oxygen saturation was set at 50% and oxygen therapy was discontinued after 12 hours. Using both Barthel and modified Rankin Scale (mRS) neurologic disability scoring systems, the patients were examined for neurologic defects at the time of discharge. Follow-up examination were repeated after six months (15).

Inclusion and exclusion criteria were as follows:

Inclusion criteria

- Age between 40 and 70 years.
- GCS >12 and patients with isolated brain damage and intact airway control.
- Ischemic and hemorrhagic stroke with no need for surgical intervention.
- Less than 12 hours have passed from the accident.
-NIHSS square between 7 and 9.

Exclusion criteria

- Patients under 40 and older than 70 years.
- Patients with diabetes mellitus, and ischemic heart disease, renal failure, acute pulmonary edema, history of massive myocardial infarction and heart failure.
- Patients who need intubation on arrival to the hospital.
- Patients with a baseline blood pressure of less than 90/60, or hypoxia.
- Patients requiring surgical intervention (i.e. acute subdural hematoma and cerebral hemorrhage).
- Patients with blood pressure greater than 170/90 in the first 12 hours of the incident.
- Patients with successful Cardiopulmonary resuscitation (CPR) within 12 hours.
- History of previous stroke or unconsciousness, resulting in the need for intubation and mechanical ventilation.
- Death or lost to follow-up.
- Patients of the control group which oxygen therapy were inevitable for them were also excluded from this study.

The sample size was calculated according to the findings of previous studies. A *t*-test was used to compare Barthel indices of the patients before and after treatment in both groups. Pearson Chi-Square test was used to compare mRS scores of case and control groups six months after treatment. General Linear Model was used for comparison of mRS scores before and after treatment.

The study protocol was reviewed and approved by the Ethics committee of Hamadan University of Medical Sciences. The study protocol was explained to the patients, and the studied patients were requested to fill written informed consent form. This RCT was registered with Iranian Registry of Clinical Trials, IRCT registration number 201212199647 N 2.

Results

There was no significant sex difference between the two groups (P = 0.5). Fourteen (53.8 %) men and 12 (46.2 %) women have entered the study group, and fourteen (56 %) men and 11 (44 %) women constituted the control group.

There was no statistically significant difference between ischemic-hemorrhagic stroke constitutions of two groups (P = 0.2). The study group consisted of 18 (69.2 %) ischemic stroke patients and 8 (30.8 %) hemorrhagic stroke cases while 20 (80 %) ischemic patients and 5 (20 %) subjects with hemorrhagic stroke were assigned to the control group.

Regarding inclusion criteria of the study, none of the patients in both groups had a history of diabetes, stroke, heart disease, and renal failure.

There was no significant difference in Barthel index scores of both groups at the follow-up examination (P=0.7) (Table 1).

Table 1. Comparison of Barthel indices before and after treatment in both groups

	Group	Number	Mean	Standard Deviation	*P*-value
Before treatment	Case	26	42.50	15.764	0.908
	Control	25	42	14.860	
After treatment	Case	24	64.58	35.230	0.437
	Control	24	56.88	32.831	

*t-test

According to the mRS scoring system, there was no difference between the patients of both groups at the time of admission (*P*=0.8), however after treatment (after six months), there were significant differences between mRS scores of the treated group compared to the controls (*P*=0.04). Higher mRS scores of the patients treated with normobaric oxygen show the better outcome of these patients compared to their controls (Table 2) (Figure 1).

Table 2. Comparison of mRS scores of case and control groups, six months after treatment

	Case		Control		Total	
	Number	Percent	Number	Percent	Number	Percent
No symptoms	6	23.1	4	16	10	19.6
No significant disability. Able to carry out all usual activities, despite some symptoms	5	19.2	1	4	6	11.8
Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities	1	3.8	5	20	6	11.8
Moderate disability. Requires some help, but able to walk unassisted	4	15.4	0	0	4	7
Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted	3	11.5	7	28	10	19.6
Severe disability. Requires constant nursing care and attention, bedridden, incontinent	2	7.7	5	20	7	13.7
Dead	5	19.2	3	12	8	15.7
Total*	26	100	25	100	51	100

*P. value= 0.041 (Pearson Chi-Square)

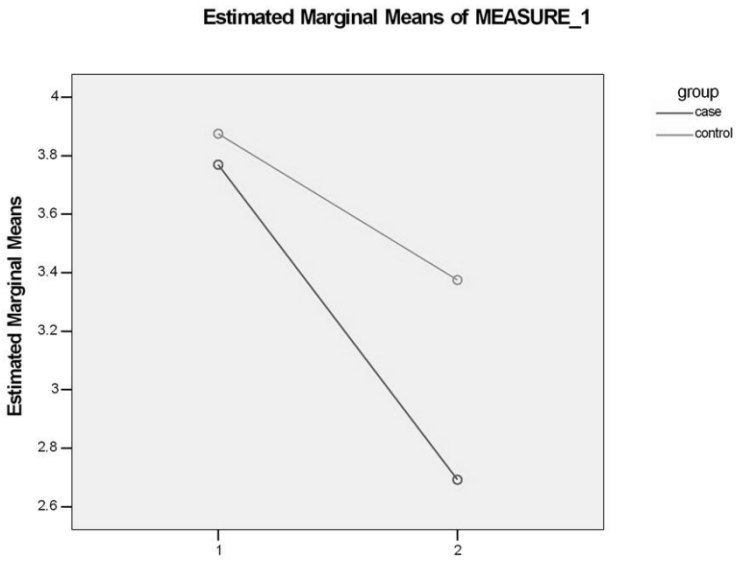

Figure 1. General Linear Model for comparison of mRS before and after treatment

Discussion

This study was designed to evaluate the effects of normobaric hyperoxia in severe acute stroke patients. According to the results of the present study, oxygen therapy in the first 12 hours of accident could improve long time outcome of patients with either ischemic or hemorrhagic stroke.

It has been shown that oxygen therapy may decrease ICP and is beneficial in the management of brain edema due to increased tissue oxygen (7,16-18), It might also stabilize the blood-brain barrier (5,6,10). Those injured brain areas that are ischemic as a result of the trauma or stroke are referred to as the "ischemic penumbra." This is the surrounding area around the central core of dead (infracted) cells. These tissues do not receive enough oxygen for normal function but do receive enough to stay alive. These brain cells have been described as “stunned”, “hibernated” or “sleeping” neurons (19,20). Penumbra protection which is discussed above is one of the other main theories for beneficial effects of oxygen therapy. Oxygen may resuscitate stunned neurons of penumbra and inhibit efface of ischemia and neural damage (21-23). As a result of the lack of ATP formation due to the lack of oxygen and nutrients, the formation of new capillaries does not occur. Due to the impaired neovascularization, the ischemic penumbra remains ischemic which in turn results in an extensive amount of brain tissue to remain ischemic and non-functioning in the chronic stroke (22,24).

It is hypothesized that oxygen therapy may also improve the function of damaged neurons in neurodegenerative diseases such as Alzheimer and other types of brain injury such as head trauma (25,26). Results of most of published studies are in line with current findings.

Oxygen therapy had a positive impact on the outcome of patients with stroke as well as radiologic findings of follow-up imaging (25); However, prolonged oxygen therapy was accompanied by oxygen intoxication and adverse effects of prolonged oxygen therapy on lungs (27). Atelectasis, ventilation-perfusion mismatch, pulmonary edema, and inflammation are among known undesirable effects of oxygen therapy. Hence, hyperoxia is suggested only in the first 24 hours after the accident. Beneficial effects of oxygen therapy with Venturi mask and 40% oxygen is also reported in another study on patients with middle cerebral artery (MCA) stroke (26). However, there are published controversial findings; results of a conducted study in Norway suggested oxygen therapy only in severe ischemic patients with an impaired ventilation function. According to their findings, oxygen therapy made no significant difference between survival and neurologic defects of patients with mild to moderate ischemic stroke (17). In another published study by Rusyniak et al., oxygen therapy had no impact on the outcome of the patients in first 24 hours, however 3 months follow-up revealed a significant difference between their studied patients. Conversely, there was the likelihood of auto reperfusion due to a high number of NIHSS scores lower than seven in their patients (16).

Larger studies are warranted to confirm present findings. Both hemorrhagic and ischemic stroke patients participated in this study, larger studies could separately compare clinical outcomes of these patients after oxygen therapy. In conclusion, according to the results of this study normobaric oxygen therapy in the first 24 hours after an accident might improve the outcome of the patients with stroke.

Acknowledgement

The authors would like to acknowledge Ladan Sadighi and Fatemeh Piriyeh for their kind contribution in conducting this study.

References

1. Willemse-van Son AH, Ribbers GM, Hop WC, et al. Community integration following moderate to severe traumatic brain injury: a longitudinal investigation. J Rehabil Med 2009;41(7):521-7.
2. De Keyser J, Sulter G, Luiten PG. Clinical trials with neuroprotective drugs in acute ischaemic stroke: are we doing the right thing? Trends in neurosciences 1999;22(12):535-40.
3. Tolias CM, Bullock MR. Critical appraisal of neuroprotection trials in head injury: what have we learned? NeuroRx 2004;1(1):71-9.
4. Glenn TC, Kelly DF, Boscardin WJ, et al. Energy dysfunction as a predictor of outcome after moderate or severe head injury: indices of oxygen, glucose, and lactate metabolism. J Cereb Blood Flow Metab 2003;23(10):1239-50.
5. Hayakawa T, Kanai N, Kuroda R, et al. Response of cereborspinal fluid pressure to hyperbaric oxygenation. J Neurol 1971;34(5):580-6.
6. Rockswold SB, Rockswold GL, Zaun DA, et al. A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. J Neurosurg 2010;112(5):1080-94.
7. Tolias CM, Reinert M, Seiler R, et al. Normobaric hyperoxia--induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: a prospective historical cohort-matched study. J Neurosurg 2004;101(3):435-44.
8. Pellerin L, Magistretti PJ. Glutamate uptake into astrocytes

stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc Natl Acad Sci U S Am 1994;91(22):10625-9.
9. Hutchinson PJ, Gupta AK, Fryer TF, et al. Correlation between cerebral blood flow, substrate delivery, and metabolism in head injury: a combined microdialysis and triple oxygen positron emission tomography study. J Cereb Blood Flow Metab 2002;22(6):735-45.
10. Ankarcrona M, Dypbukt JM, Bonfoco E, et al. Glutamate-induced neuronal death: a succession of necrosis or apoptosis depending on mitochondrial function. Neuron 1995;15(4):961-73.
11. Verweij BH, Muizelaar JP, Vinas FC, et al. Impaired cerebral mitochondrial function after traumatic brain injury in humans. J Neurosurg 2000;93(5):815-20.
12. Verweij BH, Muizelaar JP, Vinas FC, et al. Improvement in mitochondrial dysfunction as a new surrogate efficiency measure for preclinical trials: dose-response and time-window profiles for administration of the calcium channel blocker Ziconotide in experimental brain injury. J Neurosurg 2000;93(5):829-34.
13. Menzel M, Doppenberg EM, Zauner A, et al. Increased inspired oxygen concentration as a factor in improved brain tissue oxygenation and tissue lactate levels after severe human head injury. J Neurosurg 1999;91(1):1-10.
14. Reinert M, Barth A, Rothen HU, et al. Effects of cerebral perfusion pressure and increased fraction of inspired oxygen on brain tissue oxygen, lactate and glucose in patients with severe head injury. Acta Neurochir 2003;145(5):341-9; discussion 349-50.
15. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. Stroke 1999;30(8):1538-41.
16. Rusyniak DE, Kirk MA, May JD, et al. Hyperbaric oxygen therapy in acute ischemic stroke: results of the Hyperbaric Oxygen in Acute Ischemic Stroke Trial Pilot Study. Stroke 2003;34(2):571-4.
17. Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. Stroke 1999;30(10):2033-7.
18. Stiefel MF, Spiotta A, Gracias VH, et al. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. J Neurosurg 2005;103(5):805-11.
19. Abate MG, Trivedi M, Fryer TD, et al. Early derangements in oxygen and glucose metabolism following head injury: the ischemic penumbra and pathophysiological heterogeneity. Neurocrit Care 2008;9(3):319-25.
20. Robertson CA, McCabe C, Gallagher L, et al. Stroke penumbra defined by an MRI-based oxygen challenge technique: 1. Validation using [14C]2-deoxyglucose autoradiography. J Cereb Blood Flow Metab 2011;31(8):1778-87.
21. Strong AJ, Dardis R. Depolarisation phenomena in traumatic and ischaemic brain injury. Adv Tech Stand Neurosurg 2005;30(1):3-49.
22. Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci 1999;22(9):391-7.
23. Takano T, Tian GF, Peng W, et al. Cortical spreading depression causes and coincides with tissue hypoxia. Nat Neurosci 2007;10(6):754-62.
24. Kellert L, Herweh C, Sykora M, et al. Loss of Penumbra by Impaired Oxygen Supply? Decreasing Hemoglobin Levels Predict Infarct Growth after Acute Ischemic Stroke: Stroke: Relevant Impact of Hemoglobin, Hematocrit and Transfusion (STRAIGHT) - An Observational Study. Cerebrovasc Dis Extra 2012;2(1):99-107.
25. Kett-White R, Hutchinson PJ, Czosnyka M, et al. Multi-modal monitoring of acute brain injury. Adv Tech Standards in neurosurgery 2002;27:87-134.
26. Chiu EH, Liu CS, Tan TY, et al. Venturi mask adjuvant oxygen therapy in severe acute ischemic stroke. Arch Neurol 2006;63(5):741-4.
27. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. Crit Care Med 2013;41(2):423-32.