THE EFFICACY OF NORMOBARIC OXYGEN THERAPY ON CLINICAL OUTCOMES IN PATIENTS WITH ACUTE ISCHAEMIC STROKE: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction*: Tissue hypoxia is a critical factor in ischaemic cell death. Oxygen therapy can increase the oxygen supply of ischemic brain tissue and improve ischemia-reperfusion injury. However, hyperbaric oxygen has deficiencies in the treatment of patients with acute ischaemic stroke. Additionally, normobaric oxygen (NBO) is controversial in the treatment of acute ischaemic stroke patients. Therefore, this study aims to analyse current data of NBO treatment on acute ischaemic stroke patients as used in the clinic.*

Materials and methods*: We searched for relevant articles from, China National Knowledge Infrastructure (CNKI), Chongqing VIP Database (VIP), WanFang Database, PubMed, Embase, and Cochrane that were published prior to June 2017. Articles of randomized controlled trials to assess the effect of NBO on patients with acute ischaemic stroke were included.*

Results*: Six articles involving 292 participants were included in this systematic review. In the included studies, three articles had a low risk of bias and were A-level evidence, and the other studies had a higher risk of bias and were only B-level evidence. Compared to controls, NBO induced more improvement in neurological recovery after stroke based on the NIHSS scale. Additionally, NBO improved daily living ability and disability of patients, but the long-term effects were not obvious. In contrast, because of the limited number of studies included, we found that NBO has no effect on the recurrence rate and mortality of patients with acute ischaemic stroke. Additionally, NBO therapy at 45 L/min is superior to other concentrations of oxygen therapy.*

Conclusion*: These results indicate that NBO can improve the health status of patients with acute ischaemic stroke.*

Keywords: *Normobaric oxygen therapy, Acute ischaemic stroke, Systematic review.*

DOI: 10.19193/0393-6384_2019_6_517

Received *November 30, 2018;* ***Accepted*** *February 20, 2019*

Introduction

The number of deaths due to cardiovascular disease is increasing worldwide as a result of population growth, the ageing of populations, and epidemiologic changes in disease[1]. The latest data on the world disease burden has shown that in the past decade of the world, the number of deaths caused by the cardiovascular disease has increased by 21.1%, and the number of deaths due to cardiovascular disease accounts for about one-third of the total number of deaths[2]. Among cardiovascular diseases, stroke is the principal cause of death and disability. According to the American Heart Association's 2017 statistics, about 795,000 people suffer from stroke every year in the United States each year. On average, one person was found stroke every 40 seconds and one person died of stroke every four minutes. Stroke has become the second leading cause of death after ischemic heart disease[3]. Ischaemic stroke is a common type of stroke. Cerebral ischaemia can lead to the death of nerve cells. Oxygen therapy may raise the oxygenation of damaged tissues, opening aerobic pathways, and rescue neuronal cell death[4-6]. Thus, oxygen therapy has a positive effect on the outcomes of patients with stroke as well as radiology findings of follow-up imaging[7].

At present, oxygen therapy in the clinic includes NBO and hyperbaric oxygen (HBO). HBO therapy is a method used to inhale 100% oxygen inside a hy-

perbaric chamber that is pressurized to greater than 1 atm[8]. NBO refers to a treatment method in which a patient takes a mask or an oxygen breathing hood to breathe high concentrations of oxygen under a normal pressure environment that uses a specific oxygen absorbing device[9].

HBO therapy has been widely used for a long time in the treatment of various clinical diseases[10-11], especially some caused by hypoxia[12]. Studies have confirmed that HBO can significantly increase the oxygen partial pressure in ischaemic brain tissue and prevent necrosis in the ischaemic brain tissue[13]. It is also considered a promising method for the treatment of acute ischaemic stroke[14-15]. Hyperbaric oxygen chambers are used in the treatment process. However, the condition of patients with acute ischaemic stroke is usually unstable. Additionally, it is difficult to receive hyperbaric oxygen therapy early. Above all, these factors limit its clinical application in acute cerebral ischaemia.

NBO therapy can be given by families or communities at once. Notably, NBO has the advantage of being simple to use, inexpensive and easy to apply in clinical practice. For patients, it is non-invasive and can effectively extend the cerebral ischaemia thrombolysis time window[16].

The clinical effect of NBO therapy on stroke patients is still controversial, although no trials have shown any evidence that NBO is detrimental (17). Only one meta-analysis has explored the effect of NBO therapy on acute stroke patients. In contrast, because these disease processes are mechanistically different, grouping acute ischaemic stroke, intracranial haemorrhage and subarachnoid haemorrhage in the analysis may confound the findings[18]. Therefore, our study aims to explore the role of NBO in the treatment of acute ischaemic stroke, especially the concentration and time of oxygen therapy. Findings from our study will facilitate the understanding of the protective effects of NBO in acute ischaemic stroke and may also provide guidance and support for clinical practitioners in treatment.

Materials and methods

Search strategy

We searched literature databases including Chinese and foreign electronic databases. The Chinese electronic databases consisted of CNKI, VIP and Wanfang. The foreign language electronic database comprised PubMed, Embase, and Cochrane. The keywords used for the search were "ischaemia" OR "focal cerebral ischaemia" OR "stroke" OR "infarct" OR "middle cerebral artery occlusion" OR "MCAO" OR "cerebrovascular disease" OR "cerebrovascular disorder" OR "cerebrovascular accident" OR "TIA" OR "transient ischaemia attack" AND "normoxia" OR "normobaric oxygen" OR "NBO". Randomized controlled trials (RCTs) that were published prior to June 2017 were included.

The inclusion and exclusion criteria

Based on PICOS recommended by the Cochrane collaboration, we decided on the following criteria:

• Participants (P): Patients were diagnosed with acute ischaemic stroke;

• Interventions (I): NBO includes the use of a nasal cannula and mask to supplement oxygen to ensure patients maintain SaO2≥95%;

• Comparisons (C): patients without NBO (oxygen only if necessary);

• Outcomes (O): National Institutes of Health Stroke Scale (NHISS), modified Rankin score (mRS scores), modified Barthel index, Barthel Index scores (BI scores), recurrence rate, mortality rate and disability.

The exclusion criteria were:

• Non-randomized controlled trial;

• Not a primary study;

• An animal study;

• Participants in the study suffer from diseases other than stroke.

Quality Assessment

The methodological quality of each study was assessed using the Australian Joanna Briggs assessment (2008). The evaluation includes ten aspects:

• Random allocation;

• Blinding of objectives;

• Allocation concealment;

• Description of the loss of follow-up;

• Blinded evaluator;

• Baseline comparison;

• In addition to intervention, whether other measures were the same;

• The measurement method of the outcome indicator;

• The measurement method of results;

• Data analysis method.

According to the ten items listed above, a low, high or unclear risk of bias was made for each outcome of the original articles through the overall risk rating. The articles were categorized as 'yes' (low bias), 'no' (high bias), or 'unclear' (undetermined

bias). If there was disagreement between two authors, the third researcher participated in the discussion and finally determined the overall quality of the article.

Data Extraction

Two authors independently extracted data from the included studies using a pre-designed data extraction table. The content of the extracted data included the title, author, publication time and journal, study site, study type, study object, sample size, inclusion criteria and exclusion criteria of patients, number of patients in the intervention group and control groups, intervention measures, intervention time, follow-up time, the results (demographic data, outcomes of major outcomes, treatment outcomes). If there were multiple groups in the study, the literature was extracted from multiple groups for analysis. Some research findings are incomplete. Therefore, quantitative analysis was abandoned, and a systematic evaluation of qualitative analysis was performed.

Results

Search results

After the electronic database search, a total of 2623 articles were retrieved (Fig 1).

After removing duplicates, irrelevant articles, and publications that that did not meet our PICOS criteria, a total of 6 RCTs published before June 2017 remained, including 3 Chinese articles[19-21] and 3 English articles[22-24].

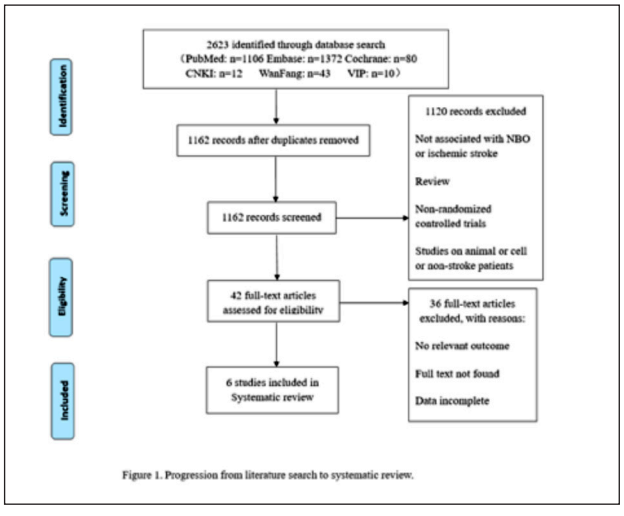

Fig. 1: Progression from literature search to systematic review.

Characteristics of the 6 RCTs

A total of 6 articles and 292 participants were included in the study. Due to the particularity of Wang Junping(2015)research design[19], the characteristics of this study will be presented (Table 1), and the others will be presented separately (Table 2). Of the 6 studies included in the study, two studies[20-21] used HBO in the observation group, and NBO was used for treatment in the control group. Three studies in the intervention group were treated with NBO[22-24], and the control group was given room air or nasal oxygen. Only one study measured time at 24 h, 48 h, and 72 h[19].

programme	Oxygen therapy time window (A)	Oxygen concentration (B)	Air circulation (C)	Duration (D)
1	1 (<20 min)	1(29%)	1(no air circulation)	1(24 h)
2	1 (<20 min)	2(45%)	2 (3 h NBO+2 h air)	2(48 h)
3	1 (<20 min)	3(61%)	3(6 h NBO+ 2 h air)	3(72 h)
4	2(20~120 min)	1(29%)	2(3 h NBO+2 h air)	3(72 h)
5	2(20~120 min)	2(45%)	3(6 h NBO+2 h air)	1(24 h)
6	2(20~120 min)	3(61%)	1 (no air circulation)	2(48 h)
7	3(>120 min)	1(29%)	3(6 h NBO+2 h air)	2(48 h)
8	3(>120 min)	2(45%)	1 (no air circulation)	3(72 h)
9	3(>120 min)	3(61%)	2(3 h NBO+2 h air)	1(24 h)

Table 1: Treatment with normobaric oxygen in patients with ischaemic stroke.

Evaluation of methodological quality

The methodological quality of the selected articles is shown (Table 3). In the 6 RCTs mentioned above, 3 studies had low risk of bias[20,22,24] and three had a high risk of bias, and the evidence provided was only Level IIb[19,21,23].

The modes of comparison group in the 6 RCT studies

The modes of NBO intervention in the 6 studies were not the same, and this difference may influence the efficacy of NBO. Two studies with intervention groups[20-21] placed patients in a 0.1 Mpa environment. Patients inhaled pure oxygen; each treatment had a pressure boost (20 min), oxygen inhalation (50 min), and decompression (20 min) for 10 times in total. The oxygen flow velocity was set at 1-3 L/min in another two articles[22,24]. In addition, Padma M et al. applied oxygen levels at 2 L/min with a face mask to maintain SaO2 ≥ 95%[23].

Amongst the included studies, one study used a special intervention method[19]. The researcher designed a programme for patients with ischaemic stroke. A total of nine measures were compared. The specific measures are shown in Table 1.

The modes of NBO intervention in the 6 RCT studies

Subjects in six studies were all acute stroke patients. The consciousness of all participants

was clear, and there were no other complications. Different concentrations and durations of oxygen therapy are factors that can affect the recovery of neurological function in patients with ischaemic stroke. The duration of primary oxygen therapy was 90 min[20-21], 8 h[22,24], 12 h[23], 24 h[19], 48 h[19], and 72 h[19]. The follow-up time in the 6 RCTs was also different. The specific differences are shown in Table 1.

Study	Characteristics of participants		Experience group		Control group		Follow-up time	Outcome indicator
	Sample size	Type of disease	Intervention measures	Sample size	Intervention measures	Sample size		
Duan Jingyu,2015 [21]	112	Acute ischaemic stroke	Under the condition of 0.1 Mpa, pure oxygen, pressure boost (20 min), oxygen inhalation (50 min), decompression (20 min), etc., once a day for a total of 1 course of treatment (10 times)	56	Under atmospheric pressure, pure oxygen for 90 minutes once a day for a total of 1 course (10 times)	56	3 months	1. NIHSS 2. recurrence rate mortality rate 3. disability
Li Weiwei,2014 [20]	110	Acute ischaemic stroke	Pure oxygen in a cabin pressure of 0.1 MPa (2 ATA), (pressurization time 20 min, oxygen inspiratory time 50 min, decompression time 20 min), 90 min/time, once/day, a total of 10 courses, 5-7 times a week.	55	Pure oxygen inhalation given in the geographical environment, 90 min/day, 10 times/treatment, 5-7 times per week.	55	3 months	1. NHISS 2. recurrence rate mortality rate 3. disability 4. mRS
Singhal AB, et al., 2005 [22]	16	Acute Ischaemic Stroke	Humidified oxygen via simple facemask at flow rates of 45 L/min	9	Room air or nasal oxygen 1 to 3 L/min if necessary to maintain SaO2 95%	7	3 months	1. NIHSS 2. mRS
Study	Characteristics of participants		Experience group		Control group		Follow-up time	Outcome indicator
	Sample size	Type of disease	Intervention measures	Sample size	Intervention measures	Sample size		
Padma MV et al., 2010 [23]	40	Acute ischaemic stroke	Humidified oxygen at flow rates of 10 L/min for 12 h	20	Under room air or oxygen at 2 L/min via a simple face mask to maintain SaO2 ≥ 95%.	20	3 months	1. NIHSS 2. Barthel Index (BI) 3. mRS
R Gilberto González et al., 2010[24]	14	Acute ischaemic stroke	Humidified oxygen via simple facemask at flow rates of 45 L/min	8	Room air or nasal oxygen 1 to 3 L/min if necessary to maintain SaO2 >95%	6	3 months	1. NIHSS 2. mRS

Table 2: Design characteristics of included studies.

First Author, year of publication	Random allocation	Research object blind method	Allocation concealment	Description of the outcome of the loss of follow-up	Evaluator blind method	Baseline comparison	Intervening measure	The measure--ment method of outcome indicator	The measure--ment method of result	Data analysis method	Quality level
Wang Junping et al., 2015[19]	unclear risk	unclear risk	unclear risk	unclear risk	unclear risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	b
Duan Jingyu, 2016[21]	unclear risk	unclear risk	unclear risk	unclear risk	unclear risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	b
Li Weiwei, 2014[20]	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	a
Singhal AB et al., 2005 [22]	unclear risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	Lower risk	a
Padma M et al., 2010[23]	unclear risk	unclear risk	unclear risk	Lower risk	Lower risk	Lower risk	unclear risk	Lower risk	Lower risk	Lower risk	b
R Gilberto González et al., 2010 [24]	Lower risk	Lower risk	unclear risk	Lower risk	Lower risk	unclear risk	unclear risk	Lower risk	Lower risk	Lower risk	a

Table 2: Methodological quality assessment of included studies.

In the oxygen therapy programme for patients with acute stroke, the oxygen therapy concentration, time window and duration of primary oxygen therapy were also different. In terms of concentration and duration of primary oxygen therapy in the experimental group, Wang Junping (2015)[19] used oxygen with volume fractions of 33%, 45%, and 61%. The durations were 24 h, 48 h, 72 h, respectively. Patients were given 90 minutes of pure oxygen inhalation once a day for 1 course (10 times) in two other studies[20,21], and a simple facemask with a humidified oxygen flow velocity of 45 L/min for 8 h was used in the remaining two studies.

Outcomes of patients in the 6 RCTs

All six studies compared the effect of normobaric oxygen on neurological recovery after stroke using the NIHSS scale[19-24]. The findings of three studies[19, 22, 24] showed that the improvement in neurological deficits in patients with NBO were better than patients in the control group. Singhal (2005)[22] in 2005 demonstrated that compared with baseline, the average NIHSS scores at 4 hours, 24 hours, and 3 months significant decreased, especially the initial 15-20 min in the first 8-hour NBO treatment. The results of Wang Junping (2015)[19] also demonstrated that 40% NBO should be applied as early as possible (<20 min) after stroke to improve the neurological function of patients. The data from Gilberto González et al., however, revealed that only 2 patients had a change of more than 4 points on the NIHSS: 1 NBO patient in whom the NIHSS dropped from 12 at baseline to 4 at 4 hours.

In contrast, Padma (2010)[23] found that NBO did not improve the clinical scores of stroke outcomes in Indian patients with AIS, as on the 7th day, the average NIHSS score of the NBO group was higher than those of the control group ($P < 0.05$). Additionally, the data from two RCTs[20, 21] demonstrated that the effect of hyperbaric oxygen on improving the degree of neurological deficit in patients with acute ischaemic stroke was better than that in the normobaric oxygen group.

Recurrence rates and mortality was assessed in two studies[20, 21]. The results showed that hyperbaric oxygen therapy and conventional oxygen therapy had no significant difference in reducing the

recurrence rate and mortality of acute ischaemic stroke (P<0.05). This result shows that HBO has no significant effect on reducing mortality and recurrence rate in acute ischaemic stroke patients, but the effect of NBO on mortality and recurrence rates needs additional study.

Two studies evaluated the activities of daily living in patients[19, 23]. The finding by Wang Junping (2015)[19] showed that patients who received 45% oxygen as soon as possible within 48 hours experienced better recovery in activities of daily living. Nonetheless, there were no significant improvements in the Barthel index score of the NBO group[23].

Four studies used mRS to measure the patients' functional recovery after stroke[20,22-24]. One study demonstrated that the mean mRS (3.7) in the NBO group improved to 2 after receiving humidified oxygen at flow rates of 10 L/min for 12 h[23], whereas in three studies, the results were the opposite. Li Weiwei[20] found that although the disability of the two groups of patients improved, the effect of HBO therapy was significantly better than NBO. Another study found that compared to the control group (4.1±1.6), the NBO group had lower scores at 3 months (3.2±2.2)[11]. Nevertheless, one study[24] found no significant correlation between mRS outcome at 3 months.

Discussion

Methodological quality analysis of the included studies

Because less than 10 studies were included in this study and the test efficiency was low, a funnel plot was not depicted, and there may be publication bias. The methodological quality level of one-two included studies was A and that of one-two was B. Randomization is required to avoid selection bias. There are four studies[19,21-23], however, that did not show how the NBO group randomized patients. Blinding is necessary to prevent outcomes from being affected by observer bias. However, two studies did not mention pertinent information about this issue. The number of studies included in this study was low, and more high-quality studies are needed to confirm the exact efficacy of NBO on acute ischaemic stroke treatment.

Effect of NBO Therapy on Acute Ischaemic Stroke Patients

NBO has several advantages; it is simple to administer, non-invasive, inexpensive, and widely available and can be used quickly and easily after stroke onset (for example, by nurses)[22]. The results from this systematic review showed that the neurological function and activities of daily living significantly improved after NBO treatment, but there is little effect on the recurrence and mortality rates of patients with acute ischaemic stroke. Thus, NBO may be a good choice and a promising strategy for acute ischaemic stroke patients.

Because of the different concentrations and durations of NBO therapy, there is some bias in evaluating the effect of NBO. Singhal(2007)[25] established a transient cerebral ischaemic model in mice using a thrombectomy method, and this study demonstrated that early implementation of oxygen is associated with a higher degree of neuroprotection. Singhal(2005)[22] found that clinical improvement was noted as early as 15 to 20 minutes after starting the 8-hour hyperoxia therapy.

The oxygen therapy time window is a significant factor that affects ischaemic stroke outcomes. In comparing treatment at 20-120 min and >120 min after the onset of ischaemic stroke, early oxygen supplementation could reduce cerebral ischaemia-reperfusion injury and benefit patients' neurological recovery[19].

Hypoxia is a key factor leading to cell death after stroke. Oxygen has various beneficial biochemical, molecular and haemodynamic applications[26-28]. Additionally, oxygen easily crosses the blood-brain barrier. However, if the concentration is low, the effect is not obvious. If the concentration is too high, the effect is adverse. If the oxygen concentration is 33% which is close to air, it has little effect on clinical results[19]. Although a high concentration of oxygen can increase the production of free radicals, it accelerates the damage of the blood-brain barrier and increases the risk of brain hypoxia. Therefore, it is very important to control the concentration of oxygen therapy. For these included studies, the effective oxygen concentration is concentrated in 45%-50%. Wang Ke(2013)showed that a 45% concentration of NBO therapy can reduce cerebral ischaemia-reperfusion injury and promote neurological recovery in rats[29]. Singhal(2005)[22] and R Gilberto González(2010)[24] also demonstrated that a 45% concentration of NBO is effective. The timing and duration of NBO therapy can affect the recovery of cerebral ischaemia-reperfusion injury. Studies have shown that early oxygen therapy is associated with increased neuroprotection within 30

minutes of onset[29]. In the included studies, oxygen therapy durations of 12 hours, 24 hours, and 48 hours all resulted in improved outcomes in ischaemic or haemorrhagic patients.

Currently, there are various definitions for the duration of oxygen therapy. However, prolonged oxygen therapy can result in oxygen intoxication and damage the lungs[30]. However, it is still unclear how long it takes for NBO to protect against cerebral ischaemia-reperfusion injury. Liu Ang(2013) explored the effect of NBO duration on cerebral ischaemia-reperfusion injury in rats at different times[31]. The results demonstrated that NBO treatment could improve neurological function and reduce infarct volume but did not increase oxidative stress and inflammation when treatment lasted 3-6 hours[31]. Short-term NBO treatment is also a safe and effective treatment for acute ischaemic stroke patients, and it has a certain significance for pre-hospital emergency care. Therefore, in future research, we should explore the risk-benefit ratio and the mechanisms of implementing NBO after different periods of cerebral ischaemia.

Limitations

First, this review only analysed the effects of NBO on neurological function recovery, activities of daily living, disability, recurrence rate, and mortality rate. We did not explore the effect of NBO on certain biochemical indexes and clinical indicators such as infarcts. Second, the low number of included studies results in a lack of persuasion and cannot support the effectiveness of NBO for patients.

Third, the analysis only included published studies, so the result of this systematic review may be exaggerated. The review only included studies in Chinese and English languages, which could also be a limitation.

Conclusion

The clinical trials investigating NBO in the treatment of patients with ischaemic stroke are scarce. The existing studies show that NBO is potentially beneficial for acute ischaemic stroke patients. Therefore, further clinical studies are needed to confirm and clarify the clinical therapeutic potential of NBO.

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Acknowledgements
This study was supported by Henan Provincial Department of Education Humanities and Social Sciences General Project. Item number: 2018-ZZJH-547, and Title of the subject: Henan province chronic disease community nursing present situation and nursing grading demand investigation and study.

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