Review Article

The Neuroprotection Effect of Oxygen Therapy: A Systematic Review and Meta-analysis

Z Deng, W Chen, J Jin, J Zhao, H Xu

Department of Orthopedics, School of Medicine, Jinling Hospital, Nanjing University, Nanjing, Jiangsu, China

Abstract

This study reviews the oxygen therapy (normobaric oxygen [NBO] and hyperbaric oxygen [HBO]) in both stroke and traumatic brain injury (TBI) patients and meta-analyzes the efficacy of two oxygen therapies in different kinds of injuries. In stroke patients, NBO showed significant improvement in reperfusion rate while there is no favorable outcome effect of HBO treatment. In patients with TBI, HBO showed significant improvement of Glasgow outcome scale score and reduction of overall mortality while NBO may play a favorable role in improving brain metabolism.

Keywords: *Hyperbaric oxygen, meta-analysis, neuroprotection, normobaric oxygen, stroke, traumatic brain injury*

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Introduction

Central nervous system (CNS) injuries, such as stroke, traumatic brain injury (TBI), spinal cord injury, and neurodegenerative diseases, are main causes of death and disability and lead to substantial economic burden around the world.[1] To minimize damage and induce recovery of salvageable tissue, various methods had been tried. For example, in stroke, more than 200 clinical trials had been completed by now, but the most effective treatment was still tissue plasminogen activator, which was introduced in 1995.[2] Inspired by more tolerance of cerebral ischemia in patients under general anesthesia,[3] medical gases, such as oxygen, hydrogen, and volatile anesthetic gases, were gradually introduced into clinical application.[4,5] Among all the medical gases, oxygen is the easiest one to get and has the widest application.

Oxygen accounts for 20.9% in air and is crucial for brain metabolism. Due to its safety, wide availability, good tolerance, and permeability through blood–brain barrier (BBB), oxygen therapy has been broadly investigated both in animal models and patients.[6] To increase oxygen supply for CNS, oxygen therapy could be divided into two types: normobaric oxygen (NBO) therapy and hyperbaric oxygen (HBO) therapy. NBO therapy is the administration of high concentrations of oxygen through a facemask at normal atmospheric pressure while HBO therapy is a treatment in which the patient breathes 100% oxygen while being exposed to environmental pressure >1 atmosphere absolute.[7]

The researches mainly concerned stroke and TBI when investigating the neuroprotective effect of oxygen, but the outcomes as well as oxygen paradigm varied among trials. Consequently, we conduct this study to review the current comparative clinical trials of oxygen therapy among nervous system injuries. The aim of our study is to compare the efficacy and safety among NBO and HBO in the situation of stroke and TBI. We hope our study could clarify the function of oxygen therapy in different kinds of nervous system injuries and give an overall view of oxygen on neuroprotection, which is hoped to be a good indicator in clinical practices.

Address for correspondence: Dr. J Zhao,
Department of Orthopedics, Jinling Hospital, School of Medicine, Nanjing University, No. 305, Zhongshan East Road, Nanjing 210002, Jiangsu, China.
E-mail: zhaojianning. 0207@163.com
Dr. H Xu,
Department of Orthopedics, Jinling Hospital, School of Medicine, Nanjing University, No. 305, Zhongshan East Road, Nanjing 210002, Jiangsu, China.
E-mail: xuhaidong1980@163.com

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Methods

Search strategy

We conducted a computer-assisted systematic search of PubMed databases from their commencement to February 2016, attempting to find all publications on clinical trials of oxygen therapy in CNS injury. Key words and medical subject heading (Mesh) terms for the search of PubMed were as follows: ("oxygen inhalation therapy" [Mesh]) OR ("hyperbaric oxygenation" [Mesh]) OR "normobaric oxygen therapy" AND ("stroke" [Mesh]) OR ("brain injuries" [Mesh]) OR "acute ischemic stroke (AIS)" OR "TBI" AND "Clinical trial". We also reviewed the bibliographies of relevant articles to identify additional studies that might have been missed.

Selection criteria

We screened titles and abstracts of identified papers to exclude studies that clearly did not meet the inclusion criteria. Full texts of those selected for further review were retrieved and evaluated. To ensure the comparability of all the studies, we set some criteria for study selection, which were as follows: (1) they were comparative studies of oxygen therapy either pre- and post-treatment or treatment and controls; (2) they must be conducted on human; animal trials and *in vitro* experiments were excluded; (3) reviews, meta-analysis, and meeting reports were excluded; (4) studies from same authors with same patients were excluded; (5) all the publications were in English and full texts could be found.

Methodological quality evaluation

We evaluated the methodological quality of all randomized controlled trials (RCT) using 7-point modified Jadad scoring system.[8] Meanwhile, observational studies, including case–control studies and cohort studies, were evaluated based on the 9-star Newcastle-Ottawa Scale.[9] 4–7 points of Jadad scoring system and 6-9 stars of Newcastle-Ottawa Scale were defined as good quality of the studies.

Data extraction

All data were extracted according to the criteria. Discrepancies were discussed and resolved by consensus. Data extracted from each study included the first author, year of publication, types of studies, regions of the population investigated, number of patients of different groups, age, gender, assessment score of nervous system, score improvement, overall mortality rate and rate of people who achieved good results, and other assessment in the studies.

Meta-analysis

STATA Statistical Software was used for all the analyses (version 12.0, STATA Corporation, College Station, TX, USA). The measure of estimated effect of interest was odds ratio or weighted mean difference with 95% confidence interval. We used two models to calculate the pooled relative risk estimates: a fixed-effects model known as the Mantel-Haenszel method[10] and a random-effects model known as the DerSimonian-Laird method.[11] We used the Cochran Q test to evaluate the heterogeneity of the studies[12] and the quantity I^2 was also calculated.[13,14] I^2 is the proportion of total variation contributed by between-study variation, and values of 25%, 50%, and 75% have been regarded as representing low, moderate, and high heterogeneity, respectively. When I^2 was over 50%, a random-effects model was used to calculate the pooled relative risk estimates. On the contrary, a fixed-effects model was used. Publication bias was evaluated to find whether the results of the studies were homogeneous. The funnel graph, the Egger regression asymmetry test,[15] and the Begg-Mazumdar adjusted rank correlation test[16] were used. When the p value of Egger's test and Begg's test is <0.05, we considered obvious bias among the studies.

Results

Search results

We found 956 records in PubMed databases and 3 records from references. With our selection criteria, 25 studies were identified in our study, including 4 studies which compared NBO and control in stroke patients,[17-20] four studies which compared HBO and control in stroke patients,[21-24] 9 studies which compared NBO treatment efficacy in TBI patients,[25-33] and 9 studies which compared HBO treatment efficacy in TBI patients [Figure 1].[27,34-41] Tables 1-4 summarize the characteristics of all the included studies.

Methodological quality evaluation results

For RCTs, there were 7 of 11 studies defined as good quality (4–7 points) [Table 5]. On the other side, for observational studies, 4 of 7 studies were defined as good quality (6–9 stars) [Table 6].

Comparison of efficacy between normobaric oxygen treatment and controls in stroke patients

Four studies were included to compare the efficacy between NBO treatment and controls in stroke patients and modified Rankin Scale (mRS), diffusion-weighted imaging (DWI) lesion volume, and reperfusion rate were analyzed. Meta-analyses indicated that NBO treatment showed significantly better efficacy than

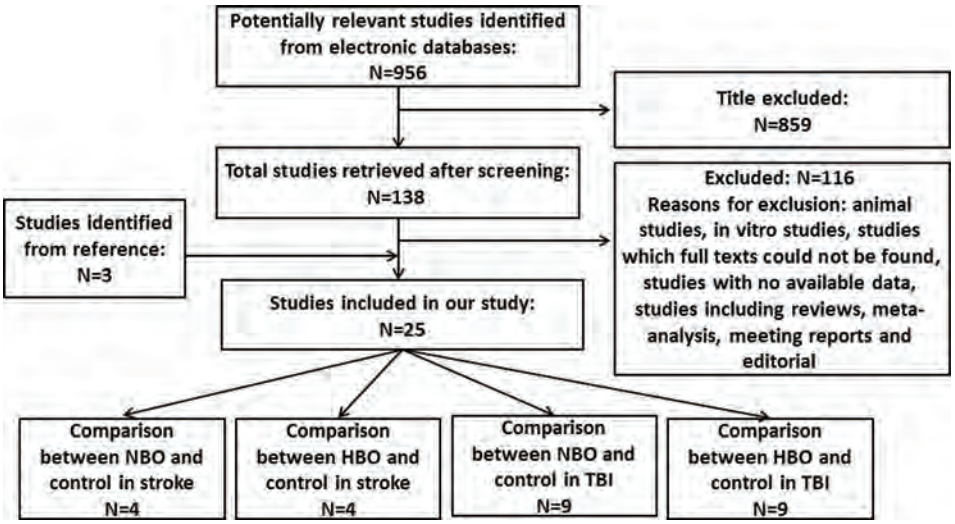

Figure 1: Scheme of research methodology

Table 1: Characteristics of studies that compared normobaric oxygen treatment and controls in stroke patients

Study	Year	Study design	Regions	Number of patients	Age (year) Mean (range)	Male (%)	Oxygen therapy protocol	FU	NIHSS Median (range)	Mean±SD mRS	Mean±SD BI	Mean±SD DWI (ml)	RR (%)
Singhal *et al*.[17]	2005	RCT	USA	NBO: 9	67	44.4	100% O_2	4 h	3	3.2±2.2		29.3±22	50
				Control: 7	37-88	42.8	45 L/min	24 h	0-19	4.1±1.6		27.1±39	0
							8 h	1 week	13				
								3 months	1-19				
Padma *et al*.[20]	2010	RCT	India	NBO: 20	55.8		100% O_2	24 h	9.4	2	73.05		
				Control: 20			10 L/min	1 week	9.05	2.2	73.8		
							12 h	3 months					
Wu *et al*.[18]	2012	RCT	USA	NBO: 10	67	50	100% O_2	4 h	14			66±42	50
				Control: 6	71	33.3	High-flow rate	24 h	9-18			41±48	0
							8 h		11				
									9-12				
Mazdeh *et al*.[19]	2015	RCT	Iran	NBO: 26		53.8	100% O_2	6 months		2.7±2.3	64.58±35.2		
				Control: 25		56	12 h			3.3±2.0	56.88±32.8		

FU=Follow-up; NIHSS=National Institutes of Health Stroke Scale; mRS=Modified Rankin Scale; BI=Barthel Index; DWI=Diffusion-weighted imaging lesion volume; RR=Reperfusion rate; RCT=Randomized control trial; NBO=Normobaric oxygen therapy; SD: Standard deviation

control in the matter of reperfusion rate while there was no statistical significant difference in mRS score and DWI lesion volume. The heterogeneity was considered low and no obvious publication bias was found [Figure 2 and Table 7].

Comparison of efficacy between hyperbaric oxygen treatment and controls in stroke patients

Four studies were included in the comparison. Mortality, favorable outcome rate, and mRS score improvement rate were involved in the meta-analysis. Improvement rate of mRS score was significantly improved in HBO treatment, while there was no difference in final mortality and favorable outcome rate. The studies involved showed low heterogeneity and no obvious bias [Figure 3 and Table 7].

Comparison of efficacy between normobaric oxygen treatment and controls in traumatic brain injury patients

A total of nine studies were included to compare the efficacy between NBO treatment and controls in TBI patients and metabolism indicators, such as intracranial pressure (ICP), brain tissue oxygen pressure (PbO_2), lactate, pyruvate and glucose, were analyzed. Meta-analysis revealed that the PbO_2 and lactate/pyruvate ratio in brain significantly increased in NBO group compared with controls, while the

Table 2: Characteristics of studies that compared hyperbaric oxygen treatment and controls in stroke patients

Study	Year	Study design	Regions	Number of patients	Age (year) Mean±SD	Male (%)	Oxygen therapy protocol	FU	NIHSS Median (range)	NIHSSi (%)	mRSi (%)	Mortality (%)	Favourable outcome (%)
Nighoghossian *et al*.[21]	1995	RCT	France	HBO: 17	53±3	53	1.5 ATA, 40 min/day 10 days	6 months				0	
				Control: 17				1 year				5.9	
Rusyniak *et al*.[22]	2003	RCT	USA	HBO: 17	75	70.6	2.5 ATA 60 min	24 h		80	81.8	5.8	37.5
				Control: 16	68	62.5		90 day		31.3	31.3	12.5	90.9
Imai *et al*.[23]	2006	CS	Japan	HBO: 19	74.9±12.1	52.6	2 ATA, 60 min/day, 7 days	7 day	18		31.5	15.7	31.5
				Control: 19	73.7±10.6	63.1		90 day	7-26		5.2	5.3	5.2
									13				
									1-21				
Chen *et al*.[24]	2012	CS	Taiwan	HBO: 16	68.3	81.2	2 ATA, 60 min/day, 10 days	10 day	4.44	93.7			
				Control: 30	68.8	50		1 month	9.31				

FU=Follow-up; NIHSS=National Institutes of Health Stroke Scale; NIHSSi=NIHSS improvement; mRSi=Modified Rankin Scale improvement; RCT=Randomized control trial; CS=Cohort study; HBO=Hyperbaric oxygen therapy; NBO=Normobaric oxygen therapy

Table 3: Characteristics of studies that compared normobaric oxygen treatment and controls in Traumatic brain injury patients

Study	Year	Study design	Regions	Number of patients	Age (year) Mean (range)	Male (%)	TBI level	Oxygen therapy protocol	GCS score Mean±SD	GOS improvement (%)	Mortality (%)	Mean±SD ICP (mmHg)	Mean±SD CCP (mmHg)	Mean±SD PbO_2 (mmHg)
Menzel *et al*.[26]	1999	CS	Germany	NBO: 12	35.5	91.6	Severe	FiO_2 60% for 3 h followed by FiO_2 100% for 3 h	5.9±1.9			15±5	73±16	88.0±114.8
				Control: 12	20-74	91.6			5.2±1.7			19±9	80±21	57.2±5.9
					33.2									
					20-50									
Magnoni *et al*.[30]	2003	Case series	Italy	8	41	75	Severe	100% oxygen for 3 h	5					35.8±16.4
					18-75									32.7±18
Tolias *et al*.[25]	2004	CS	Switzerland	NBO: 52	34.2	76.9	Severe	100% FiO_2 for 24 h	5.8			12.13±0.75		57.04±4.5
				Control: 112	16-74				5.2			15.03±0.8		34.3±1.3
					35.0									
					16-90									
Diringer *et al*.[28]	2007	Case series	USA	5	34, 18-50	60	GCS 3-9	100% oxygen						
Nortje *et al*.[29]	2008	Case series	UK	11	42	72.7	Severe		5	9.1	27.3			57±47
					17-64									28±21

Contd...

Table 3: Contd...

Study	Year	Study design	Regions	Number of patients	Age (year) Mean (range)	Male (%)	TBI level	Oxygen therapy protocol	GCS score Mean±SD	GOS improvement (%)	Mortality (%)	Mean±SD ICP (mmHg)	CCP (mmHg)	PbO_2 (mmHg)
Rockswold *et al.*[27]	2010	RCT	USA	NBO: 21	37	80.9	Severe	100% O_2 for 3 h, 3 days	5.9			11.4±0.7		29.7±2.0
				Control: 22	36				6.0			11.3±0.8		28.9±2.1
Figaji *et al.*[32]	2010	Case series	South Africa	28	5.8		Severe			41.7	12.5			31.3(25.2-38.8)
Vilalta *et al.*[31]	2011	Case series	Spain	30	27	70		FiO_2 100% for 2 h	6	59.3	20	9.9±5.3		97.7±42
					17-59							10.4±6.3		26.9±9.9
Quintard *et al.*[33]	2015	Case series	Switzerland	36	40	64.7	Severe		6	25	38.5	13±8	73±9	26±8

Study	Comparison	Mean±SD Lactate (mmol/L)	Pyruvate (umol/L)	L/P ratio	Glucose (mmol/L)	Glutamate (umol/L)	CBF (ml/100 ml/min)	CBV (ml/100 ml)	OEF (%)	CMO_2 (ml/100 g/min)
Nortje *et al.*[29]	Baseline	3.3±2.1	95±47	34.1±9.5			26	4.4	38	
	Hyperoxia	3.3±2.4	98±60	32.5±9.0			28	4.3	38	
Diringer *et al.*[28]	Baseline						39±12	3.2±0.7	39±7	1.9±0.6
	Hyperoxia						38±10	3.1±0.8	37±4	1.9±0.8
Menzel *et al.*[26]	Baseline	1.282±0.885			0.559±0.392					
	Hyperoxia	1.106±0.787			0.941±0.477					
Magnoni *et al.*[30]	Baseline	3.21±2.77	153±56	19±12	2.28±1.35					
	Hyperoxia	2.89±2.53	143±49	18±12	2.22±1.38					
Quintard *et al.*[33]	Baseline			30±8		6.0				
	Hyperoxia					22.1				
Tolias *et al.*[25]	Baseline	0.935±0.0532	21.6±2.5	41.6±6	0.609±0.047	51.48±26.05				
	Hyperoxia	0.651±0.0155	18.69±0.9	44.5±2.9	0.276±0.008	3.12±2.5				

Contd...

Table 3: Contd...

Study	Comparison	Mean±SD								
		Lactate (mmol/L)	Pyruvate (umol/L)	L/P ratio	Glucose (mmol/L)	Glutamate (umol/L)	CBF (ml/100 ml/min)	CBV (ml/100 ml)	OEF (%)	CMO_2 (ml/100 g/min)
Vilalta *et al.*[31]	Baseline	2.8	120	23.2	1.2					
	Hyperoxia	3.2	120	23.7	1.7					
Rockswold *et al.*[27]	Baseline	2.93±0.20		26.5±1.6			55.8±3.3			2.50±0.13
	Hyperoxia	3.14±0.21		30.8±2.2			54.2±3.1			2.51±0.16

NBO=Normobaric oxygen therapy; TBI=Traumatic brain injury; GCS=Glasgow Coma Scale; GOS=Glasgow Outcome Score; ICP=Intracranial pressure; CCP=Cerebral perfusion pressure; PbO_2=Brain tissue oxygen pressure; CS=Cohort study; RCT=Randomized control trial; FiO_2=Fraction of inspiration O_2; L/P ratio=Lactate/pyruvate ratio; CBF=Cerebral blood flow; CBV=Cerebral blood volume; OEF=Oxygen extraction fraction; $CMRO_2$=Cerebral metabolic rate for oxygen

Table 4: Characteristics of studies that compared Hyperbaric oxygen treatment and controls in traumatic brain injury patients

Study	Year	Study design	Regions	Number of patients	Age (year) Mean±SD	Male (%)	TBI level	Oxygen therapy protocol	FU	GCS score		GOSi (%)	Mortality (%)	ICP (mmHg)	PbO_2 (mmHg)
										Pre	Post				
Rockswold *et al.*[38]	1992	RCT	USA	HBO: 84	32	77	Severe	1.5 ATA, every 8 h for 1 h, 2 weeks		6.2			17		
				Control: 82	33	71				6.2			32		
Ren *et al.*[37]	2001	RCT	China	HBO: 35	34.0±10.4	71.4	Severe	0.25 MPa 100% O2, 40-60 min, 40 times in 2 weeks		5.1±1.7	10.1	83.7	26.3		
				Control: 20	36.5±12.3	85				5.3±1.1	8.1	30	70		
Lin *et al.*[36]	2008	CS	Taiwan	HBO: 22	25-64: 59.1%	86.4	Moderate to severe	2 ATA 100% oxygen, 2 h once a day for 20 days over 4 weeks	6 months	11.1	13.5	54.5%			
				Control: 22	25-64: 72.7%	86.4				10.4	11.5	40.9%			

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Table 4: *Contd...*

Study	Year	Study design	Regions	Number of patients	Age (year) Mean±SD	Male (%)	TBI level	Oxygen therapy protocol	FU	GCS score Pre	GCS score Post	GOSi (%)	Mortality (%)	ICP (mmHg)	PbO_2 (mmHg)
Adamides *et al.*[39]	2009	CS	Australia	HBO: 20	39.0±3.2		Severe	Depend on brain tissue oxygen monitor		6.5±0.7				13.4±0.7	31.0±1.7
				Control: 10	32.0±4.2					7.1±0.8				16.7±1.0	31.8±3.4
Mao *et al.*[35]	2010	CS	China	HBO: 30	40.9±16.4	73.3	Severe		90 day	6.0±1.1	12.6±2.1				
				Control: 30	39.8±11.5	66.7				6.3±1.3	10.1±2.8				
Rockswold *et al.*[27]	2010	RCT	USA	HBO: 26	34	88.4	Severe	1.5 ATA, 60 min, 3 days		5.6				13.0±0.7	28.6±1.6
				Control: 22	36	81.8				6.0				11.3±0.8	28.9±2.1
Rockswold *et al.*[34]	2013	RCT	USA	HBO + NBO: 19	33	83.3	Severe	1.5 ATA 100% oxygen, 1 h followed by 1.0 ATA 3 h	6 months	5.6		58	16	11.3±1.4	31.7±3.6
				Control: 21	36	80				6.0		33	42	11.3±0.9	28.9±2.7

Study	Year	Study design	Regions	Number of patients	Age (year) Mean±SD	Male (%)	Duration (m)	TBI level	Oxygen therapy protocol	Memory	Executive function	Attention	IPS
Boussi-Gross *et al.*[40]	2013	RCT	Canada	32	42.5±12.6	34	34.6±16.7	Mild	1.5 ATA	96.54±17.18	96.96±11.69	95.3±12.9	95.04±13.75
									100% oxygen, 60 min, 40 session (5 day/week)	82.43±14.74	88.26±14.74	85.13±20.28	85.12±15.88
Tal *et al.*[41]	2015	CCS	Israel	10	33.7±3.4	60	10.3±3.2	Mild to severe	1.5 ATA	78.2±7.7	84.9±3.0	88.6±3.9	78.9±5.2
									100% oxygen, 60 min, 5 day/week, 50-70 session	85.3±8.4	90.2±4.0	93.6±3.3	88.5±5.5

HBO=Hyperbaric oxygen therapy; TBI=Traumatic brain injury; FU=Follow-up time; GCS=Glasgow Coma Scale; GOSi=Glasgow Outcome Score improvement; ICP=Intracranial pressure; PbO_2=Brain tissue oxygen pressure; RCT=Randomized control trial; CS=Cohort study; NBO=Normobaric oxygen therapy; IPS=Information processing speed; CCS=case control study

Table 5: Assessment of methodological quality of randomized control trials using 7-point modified Jadad scoring system

Study	Randomization	Allocation concealment	Blinding (observer)	Blinding (patient)	Withdrawals and dropouts	Jaded score
Rockswold *et al*. 1992[38]	2	0	0	1	1	4
Nighoghossian *et al*. 1995[21]	1	0	0	0	1	2
Ren *et al*. 2001[37]	1	0	0	0	0	1
Rusyniak *et al*. 2003[22]	2	2	1	1	1	7
Singhal *et al*. 2005[17]	2	2	0	1	1	6
Padma *et al*. 2010[20]	2	2	0	1	1	6
Rockswold *et al*. 2010[27]	2	2	1	1	1	7
Wu *et al*. 2012[18]	1	0	0	0	1	2
Rockswold *et al*. 2013[34]	2	2	1	1	1	7
Boussi-Gross *et al*. 2013[40]	2	2	1	1	1	7
Mazdeh *et al*. 2015[19]	1	0	0	0	1	2

RCT=Randomized control trial

Table 6: Methodological quality of included observational studies based on 9-star Newcastle-Ottawa Scale

CS	Selection			Comparability			Outcome		Total score
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Control for important factor or additional factor	Assessment of outcome	Follow-up long enough for outcome to occur	Adequacy of follow-up cohort	
Menzel *et al*. 1999[26]	*	*	*		*	*			5
Tolias *et al*. 2004[25]	*	*	*	*	*	*			6
Imai *et al*. 2006[23]	*	*	*			*	*	*	6
Lin *et al*. 2008[36]	*	*	*		*	*			5
Adamides *et al*. 2009[39]	*	*	*	*	*	*			6
Chen *et al*. 2012[24]	*	*	*	*		*			5

CCS	Selection			Comparability			Exposure		Total score
	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for important factor or additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	
Tal *et al*. 2015[41]	*	*	*	*	*	*	*		7

CS=Cohort study; CCS=Case control study

ICP, lactate, and glucose had no significant difference between groups. Due to different machine to monitor the metabolic indicators in brain, the heterogeneity among studies was large and there might have been some kind of publication bias [Figure 4 and Table 7].

Comparison of efficacy between hyperbaric oxygen treatment and controls in traumatic brain injury patients

Nine studies were pooled in the meta-analysis and brain metabolism, cognitive function, and outcome were

Table 7: Results of meta-analysis in our study

	Number of studies	Assessment	Model, pooled relative risk estimates (95% CI)	Heterogeneity			Publication bias	
				χ^2	I^2%	*P*	Begg's *P*	Egger's *P*
NBO versus control in stroke patients	2	mRS score	Fixed, WMD−0.69 (−1.68-0.31)	0.790	0.0	0.790	0.317	-
	2	DWI lesion volume	Fixed, WMD 9.63 (−16.86-36.12)	0.63	0.0	0.429	0.317	-
	2	Reperfusion rate	Fixed, OR 12.64 (1.40-114.41)	0.00	0.0	0.980	0.317	-
HBO versus control in stroke patients	2	mRS improvement	Fixed, OR 9.34 (2.49-35.73)	0.02	0.0	0.880	0.317	-
	3	Mortality	Fixed, OR 0.98 (0.25-3.79)	1.92	0.0	0.384	0.602	0.520
	2	Favorable outcome	Random, OR 1.47 (0.06-36.33)	5.91	83.1	0.015	0.317	-
NBO versus control in TBI patients	4	ICP	Random, WMD−1.49 (−3.86-0.87)	132.14	97.7	0.00	0.497	0.919
	6	PbO_2	Random, WMD 24.21 (9.04-39.39)	664.04	99.2	0.00	0.851	0.573
	5	Lactate	Random, WMD−0.07 (−0.47-0.33)	61.99	93.5	0.00	1.000	0.438
	3	Pyruvate	Fixed, WMD−2.91 (−3.43-−2.39)	0.14	0.0	0.933	0.602	0.103
	4	Lactate/pyruvate	Fixed, WMD 3.62 (2.75-4.49)	4.75	36.8	0.191	0.174	0.036
	3	Glucose	Random, WMD 0.19 (−0.82-1.19)	46.84	95.7	0.00	0.602	0.477
HBO versus control in TBI patients	3	ICP	Random, WMD−0.53 (−3.53-2.48)	145.53	98.6	0.00	0.602	0.949
	3	PbO_2	Random, WMD 0.52 (−1.50-2.55)	8.17	75.5	0.017	0.602	0.435
	3	GOS improvement	Random, OR 3.7 (1.23-11.11)	4.58	56.3	0.101	0.117	0.429
	3	Mortality	Fixed, OR 0.31 (0.18-0.56)	2.24	10.8	0.326	0.602	0.413
	2	Memory	Fixed, WMD 10.24 (4.99-15.49)	1.69	41.0	0.193	0.317	-
	2	Executive function	Fixed, WMD 5.93 (3.13-8.73)	0.85	0.0	0.356	0.317	-
	2	Attention	Fixed, WMD 5.65 (2.69-8.61)	1.29	22.7	0.255	0.317	-
	2	Information processing speed	Fixed, WMD 9.69 (5.75-13.64)	0.01	0.0	0.942	0.317	-

NBO=Normobaric oxygen therapy; HBO=Hyperbaric oxygen therapy; mRS=Modified Rankin Scale; TBI=Traumatic brain injury; ICP=Intracranial pressure; PbO_2=Brain tissue oxygen pressure; GOS=Glasgow Outcome Score; DWI=Diffusion-weighted imaging; WMD=Weighted mean difference; CI=Confidence interval; OR=Odds ratio

taken into consideration. Results showed that HBO treatment significantly improved the Glasgow outcome scale (GOS) score and reduced overall mortality in patients with severe TBI compared with controls. In patients with mild TBI, HBO showed function alleviating the cognitive disorder after trauma, including

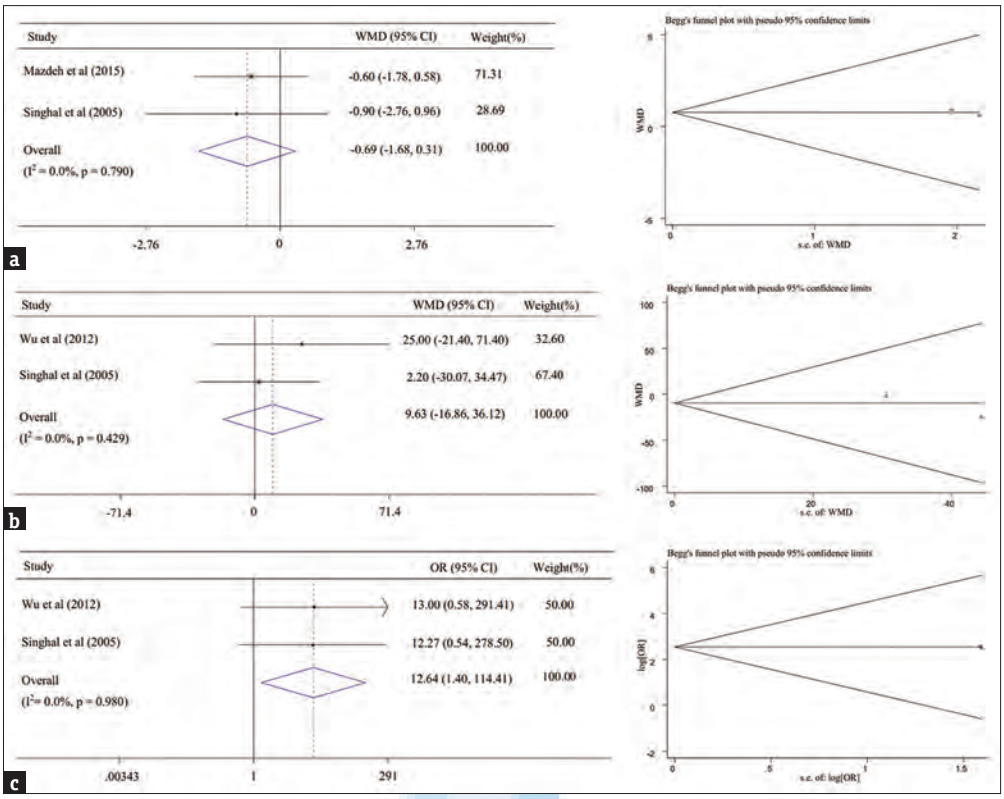

Figure 2: Forest plots and Begg's funnel plots of studies comparing normobaric oxygen treatment with controls in patients with stroke. (a) Forest plot and Begg's funnel plots conducted using modified Rankin Scale score. (b) Forest plot and Begg's funnel plots conducted using diffusion-weighted imaging lesion volume. (c) Forest plot and Begg's funnel plots conducted using reperfusion rate

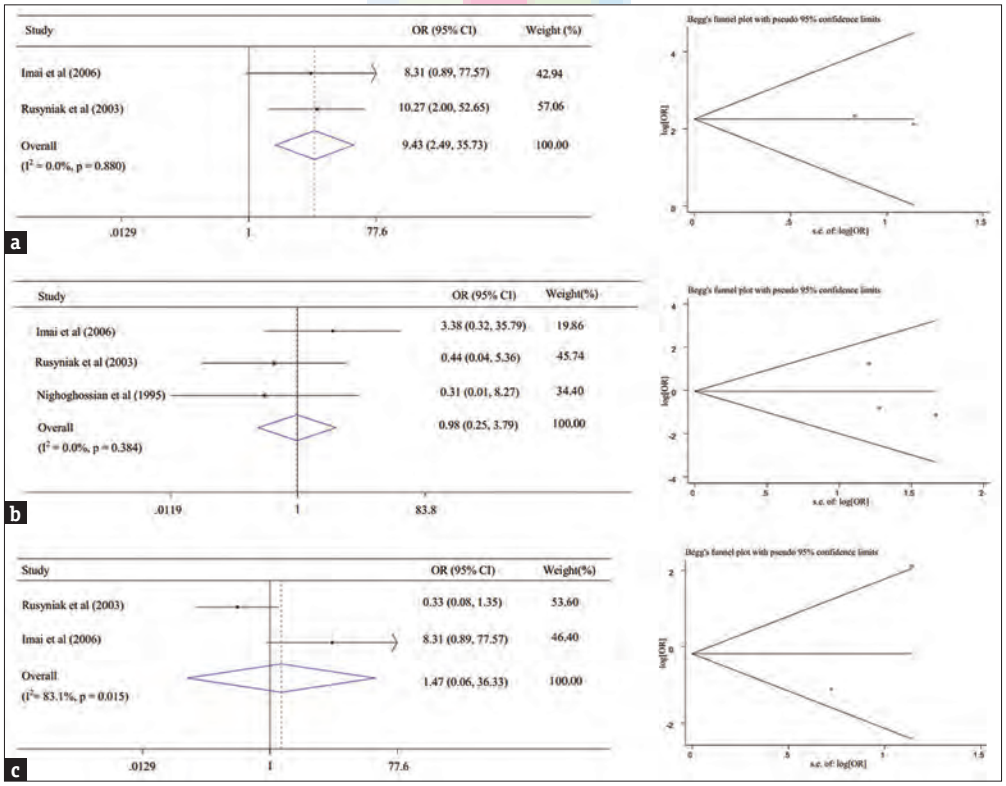

Figure 3: Forest plots and Begg's funnel plots of studies comparing hyperbaric oxygen treatment with controls in patients with stroke. (a) Forest plot and Begg's funnel plots conducted using modified Rankin Scale score improvement rate. (b) Forest plot and Begg's funnel plots conducted using mortality. (c) Forest plot and Begg's funnel plots conducted using favorable outcome rate

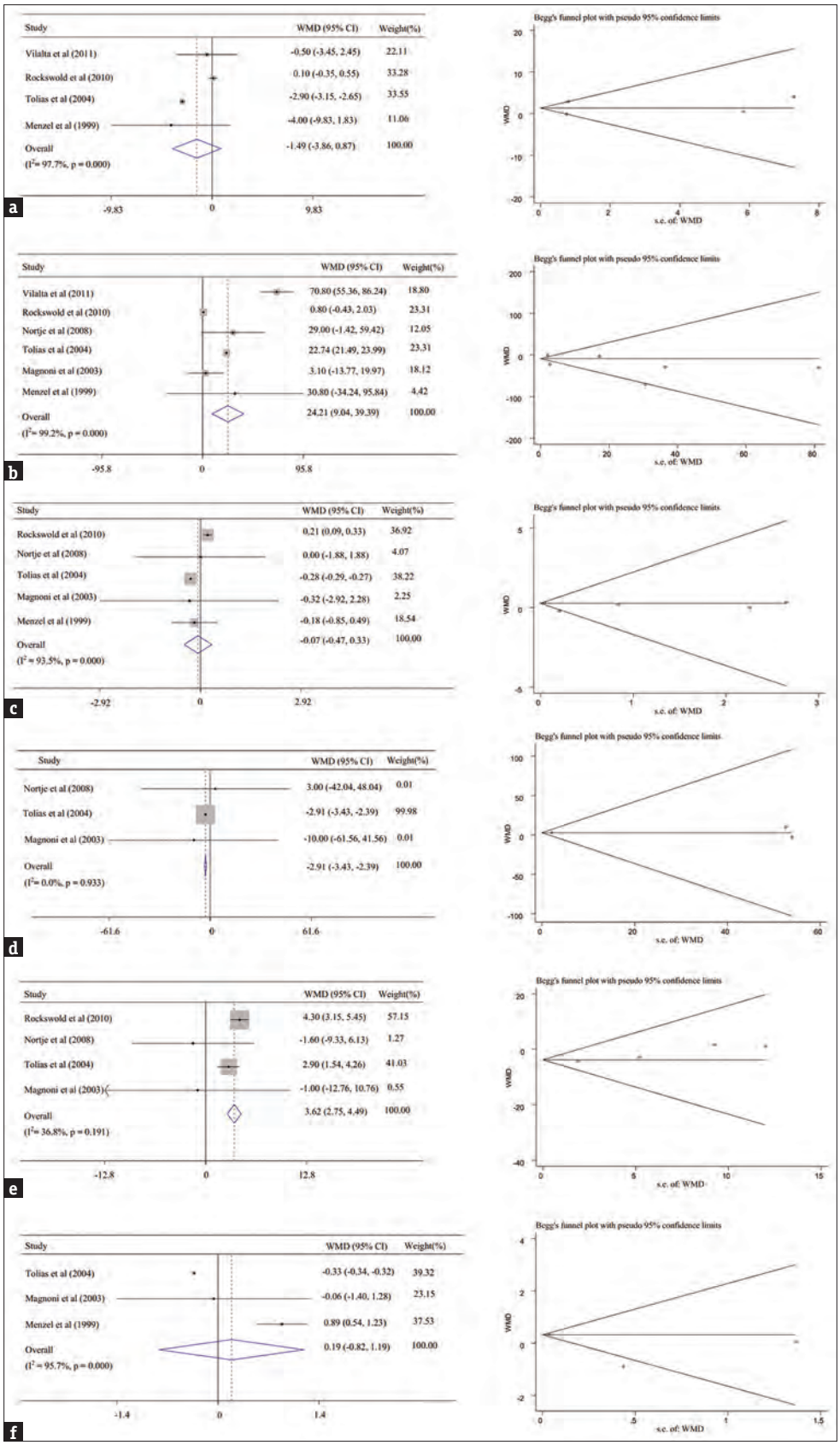

Figure 4: Forest plots and Begg's funnel plots of studies comparing normobaric oxygen treatment with controls in patients with traumatic brain injury. (a) Forest plot and Begg's funnel plots conducted using intracranial pressure. (b) Forest plot and Begg's funnel plots conducted using brain tissue oxygen pressure. (c) Forest plot and Begg's funnel plots conducted using lactate. (d) Forest plot and Begg's funnel plots conducted using pyruvate. (e) Forest plot and Begg's funnel plots conducted using lactate/pyruvate ratio. (f) Forest plot and Begg's funnel plots conducted using glucose

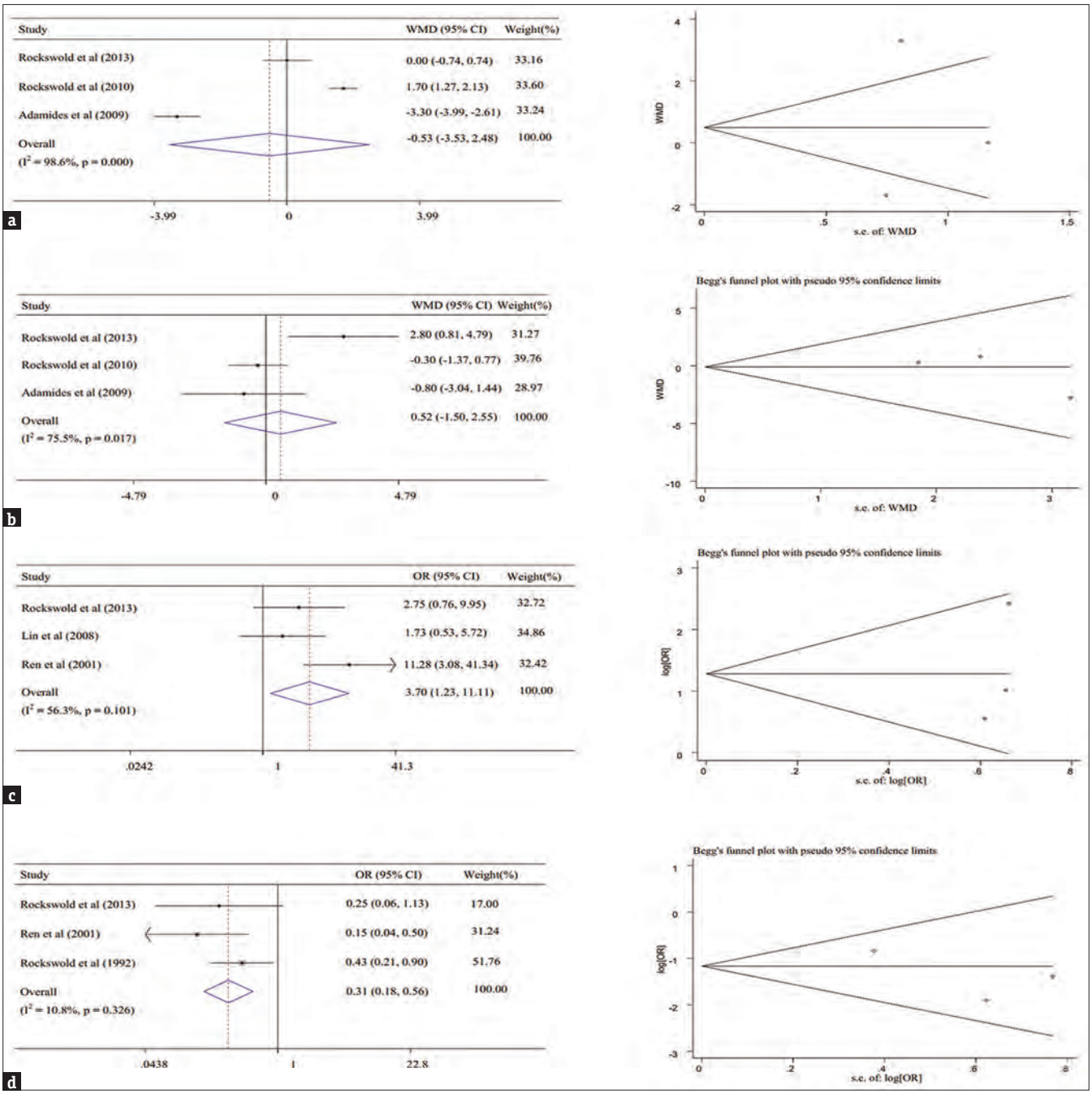

Figure 5: Forest plots and Begg's funnel plots of studies comparing hyperbaric oxygen treatment with controls in patients with traumatic brain injury. (a) Forest plot and Begg's funnel plots conducted using Glasgow outcome scale improvement rate. (b) Forest plot and Begg's funnel plots conducted using mortality. (c) Forest plot and Begg's funnel plots conducted using intracranial pressure. (d) Forest plot and Begg's funnel plots conducted using brain tissue oxygen pressure

memory, executive function, attention, and information processing speed. Studies analyzing cognitive function showed low heterogeneity with no bias, while the outcome of studies for analyzing brain metabolism had large heterogeneity but no obvious publication bias [Figures 5, 6 and Table 7].

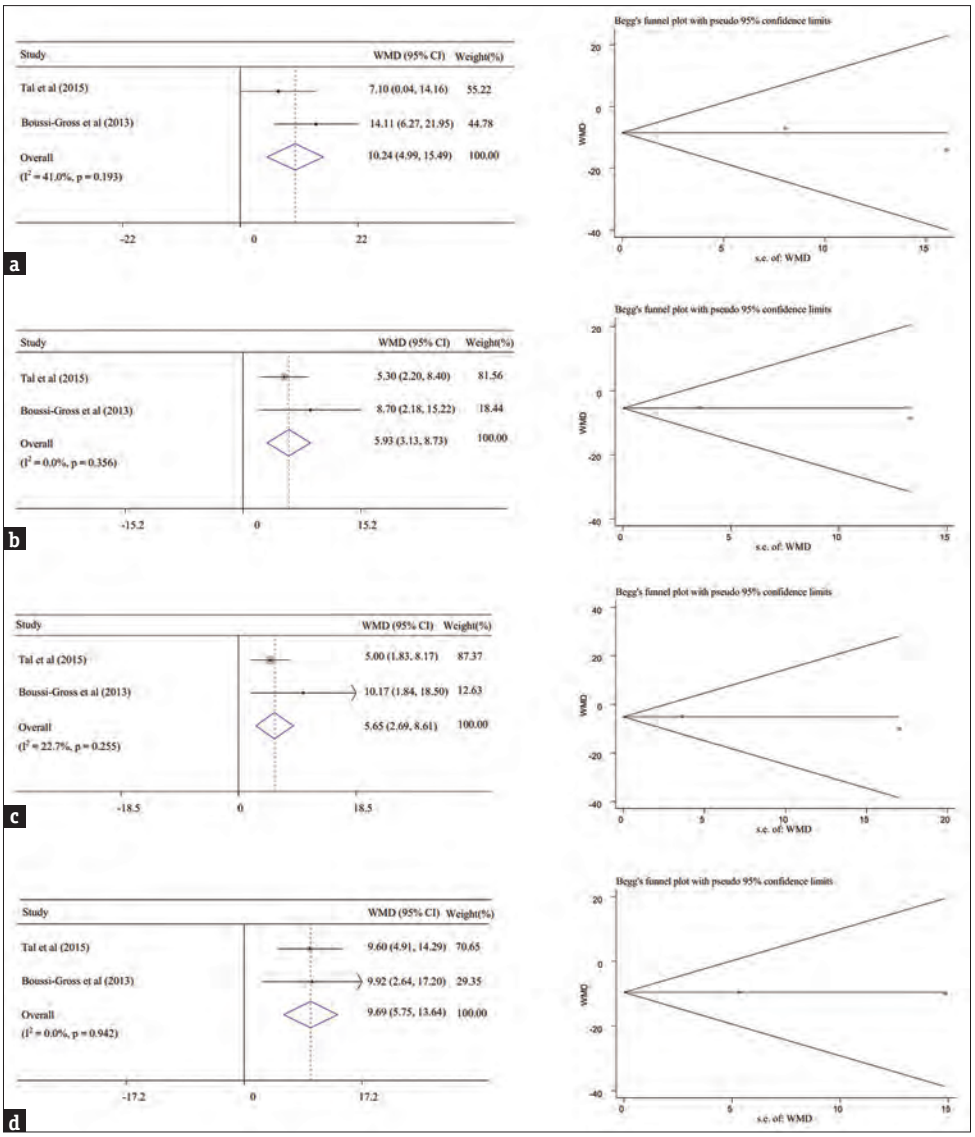

Figure 6: Forest plots and Begg's funnel plots of studies comparing hyperbaric oxygen treatment with controls in patients with traumatic brain injury. (a) Forest plot and Begg's funnel plots conducted using memory. (b) Forest plot and Begg's funnel plots conducted using executive function. (c) Forest plot and Begg's funnel plots conducted using attention. (d) Forest plot and Begg's funnel plots conducted using information processing speed

Discussion

Central nervous injury, including brain injury and spinal cord injury, could result in acroparalysis, paralysis, and even death. Effective treatment to protect nerves from injury and improve overall outcome was always required. Oxygen therapy, due to its availability and safety, had been applied in protection of nervous systems for decades.

Stroke is a leading cause of disability and death in adult and AIS is the main component in it. Brain has low antioxidant defenses and is vulnerable to hypoxia, where improving oxygen supply by oxygen therapy could be a rational treatment. Both NBO and HBO are effective methods to administer high concentrations of oxygen to brain tissue while each of them has advantages. NBO therapy had hemodynamic benefit in acute stroke patients. Singhal *et al*. conducted high-flow oxygen therapy via facemask for 8 h in patients with acute stroke (<12 h) and found that mean relative diffusion MRI lesion volumes were significantly reduced at 4 h compared with control group[17] which were consistent with following study.[18] Apart from hemodynamic effect, NBO can also benefit cerebral metabolism and prognosis. NBO improves aerobic metabolism and preserves neuronal integrity in the acute ischemic brain by detecting lactate and N-acetyl-aspartate levels before, during, and after therapy.[42] NBO therapy could result in preferable outcome, such as less mortality and comorbidities in patients experienced severe AIS[19,43] However, in Indian population, Padma *et al*. revealed that NBO did not improve the clinical scores of

stroke outcome in patients with AIS.[20] In the present meta-analysis, significant improvement in reperfusion rate was revealed in NBO group compared with control group. NBO therapy appears a promising therapy for short-lasting ischemia and is attractive clinically as it could be started at home in at-risk patients or in the ambulance in subjects suspected of transient ischemic attack/early stroke.[44] On the other hand, several trials had been conducted to explore the effect of HBO in stroke patients. Anderson first administered a double-blind prospective protocol to 39 patients with acute ischemic cerebral infarction, and found no effect of HBO treatment.[45] Subsequent trials had opposite results, which shown a favorable effect on stroke patients.[46-48] On account of small number of patients in each group, the validity of HBO in stroke patients is still to be considered. In the present study, no favorable outcome effect of HBO treatment was observed in stroke patients. Furthermore, recent meta-analysis concerning association between arterial hyperoxia and outcome, more favorable outcome was shown for NBO.[49,50]

TBI is the main cause of morbidity and mortality among young people and often result in unfavorable outcome due to damage to the CNS. Apart from the damage to blood vessels and axonal shearing induced by mechanical brain tissue injury, second injury induced by mitochondrial dysfunction, neuronal degeneration, inflammation, BBB dysfunction, and tissue hypoxia could lead brain cell to death after trauma.[51] Among those factors, cerebral hypoxia had been considered a key role in the process and oxygen therapy was a reasonable treatment to normalize aerobic metabolism and increase survival of neural tissue. Tolias *et al*. performed a prospective study of 52 patients with severe TBI and found the biochemical markers (such as glucose, glutamate, and lactate levels) in the brain in the NBO treatment group had a significant improvement compared with controls.[25] Several studies had similar results.[29,52] Using positron emission tomography to directly measure the cerebral metabolic rate for oxygen, Diringer found that NBO did not improve brain oxygen metabolism,[28] which was also proved by oxygen-15 positron emission tomography scanning.[29] In the present study, NBO treatment was observed to be able to increase PbO_2 and lactate/pyruvate ratio in brain significantly and might play a favorable role in the treatment of TBI patients. Figaji *et al*. found that hyperoxia increased arterial partial pressure of oxygen (PaO2) as well as PbO_2 significantly in TBI patients and the oxygen reactivity index (PbO_2: PaO_2 ratio) was inversely related to outcome.[32] Together with results of other studies, the baseline metabolic state of the injured brain should be taken into account when applying NBO therapy to patients with TBI.[31] At the same time, recent study revealed that incremental normobaric inspired fraction of oxygen (FiO2) levels were associated with increased cerebral excitotoxicity in patients with severe TBI, independent from PbO_2 and other important cerebral and systemic determinants,[33] which suggested us to focusing on the dose of oxygen in the following investigation.

HBO therapy had been shown to be effective in TBI patients in terms of metabolism, oxygen toxicity, ICP, cognition, and quality-of-life, along with significant improvements in single-photon emission computed tomography imaging.[27,53] Rockswold compared HBO and NBO treatment effects in severe TBI and found that HBO had a more robust posttreatment effect than NBO on oxidative cerebral metabolism and oxygen treatment for severe TBI was not an all or nothing phenomenon but represented a graduated effect.[27] In the following clinical trial, they evaluated the combination of HBO and NBO as a single treatment. Compared with standard care (control treatment), combined HBO/NBO treatments significantly improved markers of oxidative metabolism in both relatively uninjured brain and pericontusional tissue, reduced intracranial hypertension, and demonstrated improvement in markers of cerebral toxicity. Significant reduction in mortality and improved favorable outcome measured by GOS were also observed in this trial, which implied that the combination of HBO and NBO therapy have potential therapeutic efficacy compared with the 2 treatments in isolation.[34] However, there was also evidence that HBO treatment could only improve the Glasgow coma scale score, but had no influence on the quality of life and prognosis.[52] In the present meta-analysis, HBO significantly improved the GOS score and reduced overall mortality in patients with severe TBI as well as alleviated cognitive function in mild TBI patients. With the evidence that no major adverse events occurred in the treatment of HBO, our results together with previous studies indicated that HBO was preferable in the treatment of TBI subjects, even at a relatively high treatment pressure.[54]

Apart from brain injuries, oxygen therapy could also be of benefit in spinal cord injuries. Recent study showed a full neurological recovery of spinal cord injury caused by surgery using immediate HBO therapy and therapeutic hypothermia.[55] Concerning spinal cord injuries, more researches were still in animal models, which showed improvement of local inflammation and reduction of apoptosis after HBO.[56]

Overall, oxygen plays an important role in neuroprotection after different kinds of central nerve system injuries. Due to its easy access and safety

to use, oxygen therapy should be well applied in clinical practice. However, as the baseline of patients varied, the most appropriate pressure, duration, and frequency of oxygen treatment should be further explored. At the same time, the sham/control group in clinical trials should be carefully selected, where the problem of null hypothesis existed resulted from the biological activity of these "sham" controls in the past researches.[57]

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Conflicts of interest

There are no conflicts of interest.

References

1. Deng J, Lei C, Chen Y, Fang Z, Yang Q, Zhang H, *et al.* Neuroprotective gases – Fantasy or reality for clinical use? Prog Neurobiol 2014;115:210-45.
2. Young AR, Ali C, Duretête A, Vivien D. Neuroprotection and stroke: Time for a compromise. J Neurochem 2007;103:1302-9.
3. Wells BA, Keats AS, Cooley DA. Increased tolerance to cerebral ischemia produced by general anesthesia during temporary carotid occlusion. Surgery 1963;54:216-23.
4. Clarkson AN. Anesthetic-mediated protection/preconditioning during cerebral ischemia. Life Sci 2007;80:1157-75.
5. Dong H, Xiong L, Zhu Z, Chen S, Hou L, Sakabe T. Preconditioning with hyperbaric oxygen and hyperoxia induces tolerance against spinal cord ischemia in rabbits. Anesthesiology 2002;96:907-12.
6. Elraiyah T, Tsapas A, Prutsky G, Domecq JP, Hasan R, Firwana B, *et al.* A systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers. J Vasc Surg 2016;63 2 Suppl: 46S-58S.e1-2.
7. Thom SR. Hyperbaric oxygen: Its mechanisms and efficacy. Plast Reconstr Surg 2011;127 Suppl 1:131S-41S.
8. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al.* Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1-12.
9. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in metaanalyses. Ottawa, Canada: Ottawa Hospital Research Institute; 2012.
10. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-48.
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
12. Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10:101-29.
13. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
16. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-101.
17. Singhal AB, Benner T, Roccatagliata L, Koroshetz WJ, Schaefer PW, Lo EH, *et al.* A pilot study of normobaric oxygen therapy in acute ischemic stroke. Stroke 2005;36:797-802.
18. Wu O, Benner T, Roccatagliata L, Zhu M, Schaefer PW, Sorensen AG, *et al.* Evaluating effects of normobaric oxygen therapy in acute stroke with MRI-based predictive models. Med Gas Res 2012;2:5.
19. Mazdeh M, Taher A, Torabian S, Seifirad S. Effects of normobaric hyperoxia in severe acute stroke: A randomized controlled clinical trial study. Acta Med Iran 2015;53:676-80.
20. Padma MV, Bhasin A, Bhatia R, Garg A, Singh MB, Tripathi M, *et al.* Normobaric oxygen therapy in acute ischemic stroke: A pilot study in Indian patients. Ann Indian Acad Neurol 2010;13:284-8.
21. Nighoghossian N, Trouillas P, Adeleine P, Salord F. Hyperbaric oxygen in the treatment of acute ischemic stroke. A double-blind pilot study. Stroke 1995;26:1369-72.
22. Rusyniak DE, Kirk MA, May JD, Kao LW, Brizendine EJ, Welch JL, *et al.* Hyperbaric oxygen therapy in acute ischemic stroke: Results of the Hyperbaric Oxygen in Acute Ischemic Stroke Trial Pilot Study. Stroke 2003;34:571-4.
23. Imai K, Mori T, Izumoto H, Takabatake N, Kunieda T, Watanabe M. Hyperbaric oxygen combined with intravenous edaravone for treatment of acute embolic stroke: A pilot clinical trial. Neurol Med Chir (Tokyo) 2006;46:373-8.
24. Chen CH, Chen SY, Wang V, Chen CC, Wang KC, Chen CH, *et al.* Effects of repetitive hyperbaric oxygen treatment in patients with acute cerebral infarction: A pilot study. ScientificWorldJournal 2012;2012:694703.
25. Tolias CM, Reinert M, Seiler R, Gilman C, Scharf A, Bullock MR. 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;101:435-44.
26. Menzel M, Doppenberg EM, Zauner A, Soukup J, Reinert MM, Bullock R. Increased inspired oxygen concentration as a factor in improved brain tissue oxygenation and tissue lactate levels after severe human head injury. J Neurosurg 1999;91:1-10.
27. Rockswold SB, Rockswold GL, Zaun DA, Zhang X, Cerra CE, Bergman TA, *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;112:1080-94.
28. Diringer MN, Aiyagari V, Zazulia AR, Videen TO, Powers WJ. Effect of hyperoxia on cerebral metabolic rate for oxygen measured using positron emission tomography in patients with acute severe head injury. J Neurosurg 2007;106:526-9.
29. Nortje J, Coles JP, Timofeev I, Fryer TD, Aigbirhio FI, Smielewski P, *et al.* Effect of hyperoxia on regional oxygenation and metabolism after severe traumatic brain injury: Preliminary findings. Crit Care Med 2008;36:273-81.
30. Magnoni S, Ghisoni L, Locatelli M, Caimi M, Colombo A, Valeriani V, *et al.* Lack of improvement in cerebral metabolism after hyperoxia in severe head injury: A microdialysis study. J Neurosurg 2003;98:952-8.
31. Vilalta A, Sahuquillo J, Merino MA, Poca MA, Garnacho A, Martínez-Valverde T, *et al.* Normobaric hyperoxia in traumatic brain injury: Does brain metabolic state influence the response to hyperoxic challenge? J Neurotrauma 2011;28:1139-48.
32. Figaji AA, Zwane E, Graham Fieggen A, Argent AC, Le Roux PD, Peter JC. The effect of increased inspired fraction

of oxygen on brain tissue oxygen tension in children with severe traumatic brain injury. Neurocrit Care 2010;12:430-7.
33. Quintard H, Patet C, Suys T, Marques-Vidal P, Oddo M. Normobaric hyperoxia is associated with increased cerebral excitotoxicity after severe traumatic brain injury. Neurocrit Care 2015;22:243-50.
34. Rockswold SB, Rockswold GL, Zaun DA, Liu J. A prospective, randomized Phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. J Neurosurg 2013;118:1317-28.
35. Mao JH, Sun ZS, Xiang Y. Observation of curative effects of hyperbaric oxygen for treatment on severe craniocerebral injury. J Clin Neurol 2010;23:386-8.
36. Lin JW, Tsai JT, Lee LM, Lin CM, Hung CC, Hung KS, *et al.* Effect of hyperbaric oxygen on patients with traumatic brain injury. Acta Neurochir Suppl 2008;101:145-9.
37. Ren H, Wang W, Ge Z. Glasgow Coma Scale, brain electric activity mapping and Glasgow Outcome Scale after hyperbaric oxygen treatment of severe brain injury. Chin J Traumatol 2001;4:239-41.
38. Rockswold GL, Ford SE, Anderson DC, Bergman TA, Sherman RE. Results of a prospective randomized trial for treatment of severely brain-injured patients with hyperbaric oxygen. J Neurosurg 1992;76:929-34.
39. Adamides AA, Cooper DJ, Rosenfeldt FL, Bailey MJ, Pratt N, Tippett N, *et al.* Focal cerebral oxygenation and neurological outcome with or without brain tissue oxygen-guided therapy in patients with traumatic brain injury. Acta Neurochir (Wien) 2009;151:1399-409.
40. Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, *et al.* Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury-randomized prospective trial. PLoS One 2013;8:e79995.
41. Tal S, Hadanny A, Berkovitz N, Sasson E, Ben-Jacob E, Efrati S. Hyperbaric oxygen may induce angiogenesis in patients suffering from prolonged post-concussion syndrome due to traumatic brain injury. Restor Neurol Neurosci 2015;33:943-51.
42. Singhal AB, Ratai E, Benner T, Vangel M, Lee V, Koroshetz WJ, *et al.* Magnetic resonance spectroscopy study of oxygen therapy in ischemic stroke. Stroke 2007;38:2851-4.
43. Chiu EH, Liu CS, Tan TY, Chang KC. Venturi mask adjuvant oxygen therapy in severe acute ischemic stroke. Arch Neurol 2006;63:741-4.
44. Ejaz S, Emmrich JV, Sitnikov SL, Hong YT, Sawiak SJ, Fryer TD, *et al.* Normobaric hyperoxia markedly reduces brain damage and sensorimotor deficits following brief focal ischaemia. Brain 2016;139(Pt 3):751-64.
45. Anderson DC, Bottini AG, Jagiella WM, Westphal B, Ford S, Rockswold GL, *et al.* A pilot study of hyperbaric oxygen in the treatment of human stroke. Stroke 1991;22:1137-42.
46. Yang X, Li K, He T. The effect of early hyperbaric oxygenation on the ability of daily life of patients with stroke. Chin J Clin Rehabil 2003;7:1221.
47. Yang Z, Chen H, Xian MJ, Jiang XD, Yuan L, Mai JH. Role of medical pressured oxygen injector in the rehabilitation of motor function and abilities of daily living at early stage of cerebral infarction. Chin J Clin Rehabi 2004;8:2414-5.
48. Renliang Zhao, Chunxia Wang, Yongjun Wang. Changes in serum cellular adhesion molecule and matrix metalloproteinase-9 levels in patients with cerebral infarction following hyperbaric oxygen therapy. A case and intergroup control study. Neural Regen Res 2008;3:1245-8.
49. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association between arterial hyperoxia and outcome in subsets of critical illness: A systematic review, meta-analysis, and meta-regression of cohort studies. Crit Care Med 2015;43:1508-19.
50. Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, *et al.* Arterial hyperoxia and mortality in critically ill patients: A systematic review and meta-analysis. Crit Care 2014;18:711.
51. Talley Watts L, Long JA, Manga VH, Huang S, Shen Q, Duong TQ. Normobaric oxygen worsens outcome after a moderate traumatic brain injury. J Cereb Blood Flow Metab 2015;35:1137-44.
52. Beynon C, Kiening KL, Orakcioglu B, Unterberg AW, Sakowitz OW. Brain tissue oxygen monitoring and hyperoxic treatment in patients with traumatic brain injury. J Neurotrauma 2012;29:2109-23.
53. Harch PG, Andrews SR, Fogarty EF, Amen D, Pezzullo JC, Lucarini J, *et al.* A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. J Neurotrauma 2012;29:168-85.
54. Wolf EG, Prye J, Michaelson R, Brower G, Profenna L, Boneta O. Hyperbaric side effects in a traumatic brain injury randomized clinical trial. Undersea Hyperb Med 2012;39:1075-82.
55. Urquieta E, Jye Poi M, Varon J. Reversal of spinal cord ischemia following endovascular thoracic aortic aneurysm repair with hyperbaric oxygen and therapeutic hypothermia. Ther Hypothermia Temp Manag 2015;6:110.
56. Mathew B, Laden G. Management of severe spinal cord injury following hyperbaric exposure. Diving Hyperb Med 2015;45:210.
57. Figueroa XA, Wright JK. Clinical results in brain injury trials using HBO2 therapy: Another perspective. Undersea Hyperb Med 2015;42:333-51.