Neurol Sci (2016) 37:693–701
DOI 10.1007/s10072-015-2460-2

ORIGINAL ARTICLE

Hyperbaric oxygen therapy for the treatment of traumatic brain injury: a meta-analysis

Fei Wang[1] · Yong Wang[1] · Tao Sun[1] · Hua-lin Yu[1]

Received: 5 July 2015 / Accepted: 21 December 2015 / Published online: 8 January 2016

Abstract Compelling evidence suggests the advantage of hyperbaric oxygen therapy (HBOT) in traumatic brain injury. The present meta-analysis evaluated the outcomes of HBOT in patients with traumatic brain injury (TBI). Prospective studies comparing hyperbaric oxygen therapy vs. control in patients with mild (GCS 13–15) to severe (GCS 3–8) TBI were hand-searched from medical databases using the terms "hyperbaric oxygen therapy, traumatic brain injury, and post-concussion syndrome". Glasgow coma scale (GCS) was the primary outcome, while Glasgow outcome score (GOS), overall mortality, and changes in post-traumatic stress disorder (PTSD) score, constituted the secondary outcomes. The results of eight studies (average age of patients, 23–41 years) reveal a higher post-treatment GCS score in the HBOT group (pooled difference in means = 3.13, 95 % CI 2.34–3.92, $P < 0.001$), in addition to greater improvement in GOS and lower mortality, as compared to the control group. However, no significant change in the PTSD score was observed. Patients undergoing hyperbaric therapy achieved significant improvement in the GCS and GOS with a lower overall mortality, suggesting its utility as a standard intensive care regimen in traumatic brain injury.

Keywords Glasgow coma scale · Glasgow outcome score · Oxygen therapy · Post-concussion syndrome · Traumatic brain injury

✉ Hua-lin Yu
hualin_yu@sina.com; neurosurgeonwf@aliyun.com

[1] The Second Department of Neurosurgery, First Affiliated Hospital of Kunming Medical University, 295 Xichang Rd, Kunming, Yunnan 650032, China

Introduction

Hyperbaric oxygen therapy (HBOT), the therapeutic administration of 100 % oxygen at environmental pressures greater than 1 atmosphere absolute, has been shown to have beneficial effects in wound healing and repair after brain injury. Hyperbaric oxygenation aims directly at hypoxia, ischemia, and edema [1], the critical factors mediating the secondary damage in traumatic brain injury (TBI). HBOT increases the oxygen supply to the brain, raises oxygen tension, decrease intracranial pressure and relieve cerebral edema [2–6]. At a cellular level, it improves metabolism, reduce apoptosis, alleviate oxidative stress and increase mitochondrial function [7–9].

Despite these advantages, HBOT is not widely adopted as a standard therapy for TBI, mainly due to concerns of its efficacy in terms of clinical outcomes, and the associated risk of damage to ears, sinuses, and lungs. Bennett et al. have shown that while HBOT reduce the risk of death and improve the final Glasgow coma scale (GCS), there was no improvement in the quality of life for the survivors [5]. Reports elsewhere also discredited the use of HBOT in TBI and post-concussion syndrome (PCS) [10–12]. However, all these reports are limited by a small sample size, variance in treatment protocols, lack of validity, and inapt choice of placebo/sham controls [5, 8, 10, 11]. The optimal oxygen dose and duration broadly vary among the studies, [8, 10, 13] making the comparison more intricate, resulting in rather skewed interpretations. Furthermore, lower oxygen pressures are shown to be effective in mild TBI in terms of metabolism, intracranial pressure, oxygen toxicity, cognition, and quality-of-life, along with significant improvements in SPECT imaging [13, 14].

Traumatic brain injury is the major cause of death and disability in younger population. In spite of the advances in

therapeutic options, the mortality rate is about 40 % in severe TBI [15]. The severity of TBI is assessed according to the duration of loss of consciousness, post-traumatic amnesia, and GCS grading of the level of consciousness [8]. Severe TBI is defined as a GCS score less than 8, while a GCS grade of 13–15 is referred to as mild TBI, often characterized by post-concussion syndrome (PCS), a set of symptoms including headache, dizziness, neuropsychiatric symptoms, and cognitive impairment. TBI accounts for more than 50,000 deaths, while 230,000 people are hospitalized and survive the injury, and an estimated 80,000–90,000 people experience the onset of long-term disability each year, in USA [16]. Considering the socioeconomic burden of TBI, along with the poor outcome of available systemic therapies, concurrence in the use of hyperbaric oxygen as an adjuvant therapy is of utmost importance.

We undertook the present meta-analysis to assess the efficacy of hyperbaric oxygen therapy and to compare the clinical outcomes with normobaric control in patients with severe to mild traumatic brain injury.

Methods

Literature search and selection criteria

A literature search of the Medline, Cochrane, EMBASE, and Google Scholar databases were performed by two independent reviewers using the terms "oxygen therapy, traumatic brain injury, and post-concussion syndrome" until December 10, 2014. In addition, the reference lists of the identified studies were also searched for eligible studies. Randomized, controlled trials or two-arm prospective studies comparing normobaric vs. hyperbaric oxygen therapy in patients with either severe (GCS score 3–8) or mild (GCS score 13–15) traumatic brain injury with PCS symptoms were included in the current meta-analysis. Only full text articles were considered for analysis. Letters, comments, editorials, case reports, proceedings, or personal communications were not included.

We did not recruit patients with stroke or any brain injury other than trauma, or patients treated with surgery or other systemic therapies. We also excluded trials that are retrospective, cohort, or studies with no quantitative primary outcome.

Data extraction

Studies identified by the search strategy were hand-selected and data extracted by two independent reviewers. Where there was uncertainty regarding eligibility, a third reviewer was consulted.

The following information was extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each treatment group, participants' age and gender, treatment protocol, changes in GCS score, rate of improvement in GOS, the overall mortality rate, and changes in PTSD score.

Outcomes

The primary outcome was the GCS score. The measurements of PCS symptoms, including GOS, overall mortality, and changes in PTSD score were the secondary outcomes.

Quality assessment

The included studies were assessed for the risk of bias using the Cochrane Collaboration's risk assessment tool [17]. Figure 5 represents the assessed outcomes of the eight studies included in the analysis.

Statistical analysis

The difference in means was calculated for changes in GCS and PTSD scores in the HBOT group, and compared to the control group. Similarly, the odds ratio was calculated for the rate of improvement in GOS and overall mortality rate, and compared among the two treatment groups. Heterogeneity among the studies was assessed by the Cochran Q and the I2 statistics. For the Q statistic, $P < 0.1$ was considered statistically significant for heterogeneity. For the I2 statistic, which indicated the percentage of the observed inter-study variability due to heterogeneity rather than chance, the suggested range is as follows, no heterogeneity (I2 = 0–25 %), moderate heterogeneity (I2 = 25–50 %), large heterogeneity (I2 = 50–75 %), and extreme heterogeneity (I2 = 75–100 %). If either Q statistics ($P < 0.1$) or I2 statistics (>50 %) indicate that heterogeneity exists between studies, then the random effects model was preferred (DerSimonian–Laird method). Otherwise, the fixed effects model (Mantel–Haenszel method) was recommended. Pooled difference in means or odds ratio was calculated and a 2-sided P value < 0.05 was considered statistically significant.

The leave-one-out approach was used to assess the sensitivity of the meta-analysis. The Egger's test was performed to assess publication bias. The funnel plot was not performed, as the number of included studies in the meta-analysis was not sufficient enough to observe publication bias in the outcomes [18]. All statistical analyses were performed using the statistical software, Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Literature search

Of the 282 studies identified by the literature search, 21 articles were chosen for full text review. After careful examination, 5 articles were excluded for having no control group, and another 8 were excluded for no quantitative outcome of interest. The remaining 8 articles were included in the final review. An outline of the search flow of studies is given in Fig. 1.

Study characteristics

Eight studies with 519 participants were included in this meta-analysis. The characteristics of these studies are summarized in Table 1. The total number of participants ranged from 20 to 84 in the HBOT group and 20 to 82 in the control group. The mean age of patients ranged from 23 to 41 years. The patient population was predominantly males (62–100 %) in the included studies. The HBO protocols used in each study were heterogeneous both in levels of oxygen administered and length and frequency of treatment. The pre-treatment GCS score was 5.1–11.1 in the HBOT group, while it ranged from 5.3 to 10.4 in the control group. The post-treatment GCS score ranged from 10.1 to 13.5 in the HBOT group, while it was 8.1-11.5 in the control group. The rate of improvement in GOS ranged from 55 to 84 % in the HBOT group, while it was only 30–41 % in the control group. The overall mortality rate was 16–26 % and 32–70 % in the HBOT and control groups, respectively. The pre-treatment PTSD score ranged from 49.4 to 50.0 in the HBOT group, while it ranged from 45.1 to 48.9 in the control group. Whereas, the post-treatment PTSD score was 41.6–42.6 and 40.6–43.9 in the HBOT and control groups, respectively.

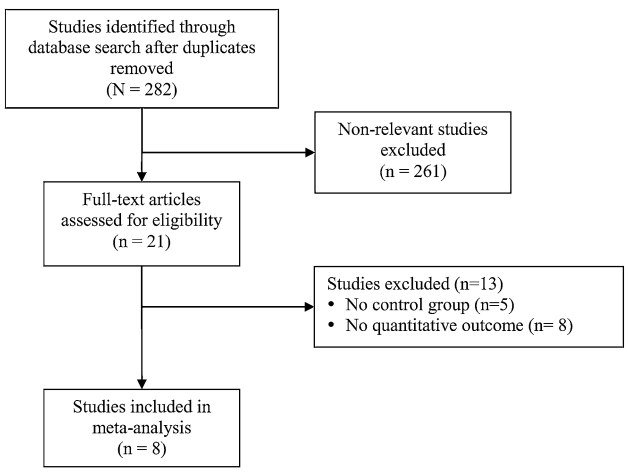

Fig. 1 Flow chart for study selection

Clinical outcome evaluation

Change in GCS score

Six studies [10, 11, 19–22] were excluded from the current analysis, as they did not report complete pre-treatment and post-treatment GCS score data. No significant heterogeneity was observed when data from the remaining 2 studies [1, 21, 23] were pooled (heterogeneity test: $Q = 0.75$, $df = 1$, $P = 0.386$, $I2 = 0$ %). Therefore, a fixed effect model of analysis was performed. The overall analysis revealed that the change in GCS score was significantly higher in the HBOT group than in the control group (pooled difference in means = 3.13, 95 % CI 2.34–3.92, $P < 0.001$; Fig. 2).

GOS improvement rate

Five studies [1, 10, 11, 22, 23] were excluded from the analysis since they had not reported the rate of improvement in GOS. Because of significant heterogeneity in the pooled data from the remaining 3 studies [19–21] (Heterogeneity test: $Q = 4.83$, $df = 2$, $P = 0.09$, $I2 = 58.56$ %), a random effects model of analysis was used. The overall analysis revealed that the HBOT group achieved a significantly higher rate of improvement in GOS when compared to the control group (pooled odds ratio = 3.78, 95 % CI 1.23–11.63, $P = 0.020$; Fig. 3a).

Overall mortality rate

Five studies [1, 10, 11, 22, 23] were excluded from the current analysis, as they did not report an overall mortality rate. No significant heterogeneity in the pooled data was observed in the rest of the 3 studies [19–21] (Heterogeneity test: $Q = 2.16$, $df = 2$, $P = 0.34$, $I2 = 7.24$ %); therefore a fixed effect model of analysis was used. The overall analysis revealed that the HBOT group achieved significantly lower overall mortality rate than the control group (pooled odds ratio = 0.32, 95 % CI 0.18–0.57, $P < 0.001$; Fig. 3b).

PTSD score change

Six studies [1, 19–23] did not report complete pre-treatment and post-treatment PTSD score data and hence were excluded from the analysis. There was no significant heterogeneity when data from the 2 studies [10, 11] were pooled (Heterogeneity test: $Q = 1.19$, $df = 1$, $P = 0.276$, $I2 = 15.80$ %); therefore, a fixed effect model of analysis was used. The overall analysis revealed that there was no significant change in the PTSD score between the HBOT and the control groups (pooled difference in means = −1.49, 95 % CI −5.79 to 2.80, $P = 0.496$; Fig. 3c).

Table 1 Summary of basic characteristics of studies included in meta-analysis

References	Comparison	Number of cases	Age, (years)[†]	Male (%)	TBI level	HBO protocol	HBOT time point after TBI	Follow-up time	GCS score		GOS improved	Overall mortality	PTSD	
									Pre[†]	Post[†]			Pre[§]	Post[§]
Cifu et al. [11]	HBOT (2.0ATA)	21	23.2 (2.95)	100	Mild	2 ATA pure oxygen, 1 h once a day for 40 times	8.5 (6.58)[†] months	10 weeks					49.39	42.56
	Control	21		100									45.14	43.90
Rockswold et al. [19]	HBOT/ NBH	20	33[§]	83.3	Severe	1.5 ATA pure oxygen, 1 h followed by, 1.0 ATA 3 h	Within 24 h	6 months	5.6[§]		58 %	16 %		
	Control	22	36[§]	80					6.0[§]		33 %	42 %		
Wolf et al. [10]	HBOT	25	28.3 (8.1)	96	Mild		3–71 months	6 weeks					50.0	41.6
	Control	25	28.4 (7.4)	96									48.9	40.6
Mao et al. [23]	HBOT	30	40.9 (16.4)	73.3	Severe (GCS < 8)		12.3 (1.5)[†] after admission	90 days	6.0 (1.1)	12.6 (2.1)				
	Control	30	39.8 (11.5)	66.7					6.3 (1.3)	10.1 (2.8)				
Lin et al. [20]	HBOT	22	25–64: 59.1 %	86.4	GCS from 3 to 12	2ATA pure 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 %			
Zeyu (2007)	HBOT	30	26[§]	61.7	Moderate to severe	0.2–0.25 MPa, 1 h once a day for 10 times	24 h to 10 days	Before and after treatment	8.2 (2.2)	12.5 (1.2)				
	Control	30							8.1 (2.1)	8.9 (2.9)				
Ren et al. [21]	HBOT	35	34.0 (10.4)	71.4	Severe	0.25 M Pa pure oxygen, 40–60 min with 10 min break, 10 times being one therapy every 4 days for 3–4 courses	ASAP after stable	[a]	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 %		
Rockswold et al. [22]	HBOT	84	32[§]	77	Severe				6.2[§]			17 %		
	Control	82	33[§]	71					6.2[§]			32 %		

Data expressed as [†] mean (standard deviation); [§] mean

ATA atmospheres absolute, *HBOT* hyperbaric oxygen therapy, *NBH* normobaric hyperoxia, *GCS* Glasgow Coma Scale, *GOS* Glasgow Outcome Score, *PTSD* posttraumatic stress disorder

[a] On the third day after injury, at the second week after one course of HBO, and in the second month after 3 courses of HBO

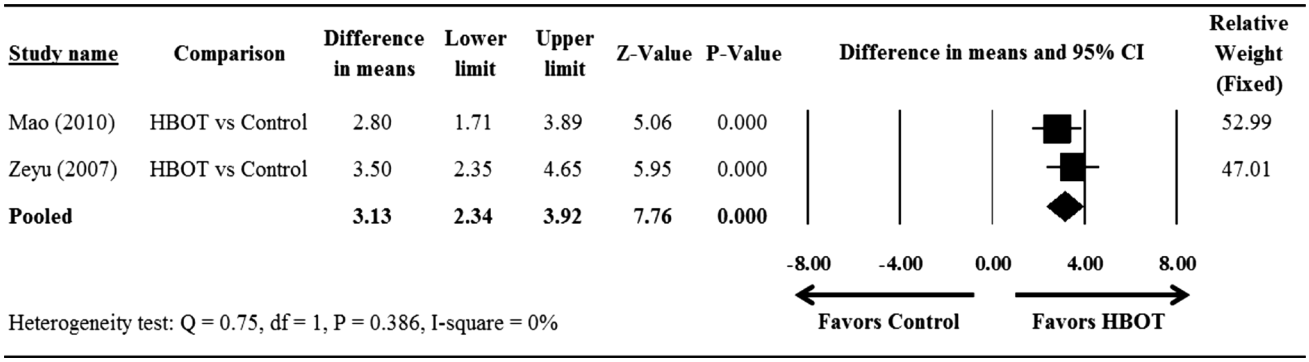

Fig. 2 Forest plots showing results for the meta-analysis of GCS score change. *CI* confidence interval, *HBOT* hyperbaric oxygen therapy, *GCS* Glasgow Coma Scale

Sensitivity analysis

The results of sensitivity analysis for the rate of improvement in GOS and overall mortality are summarized in Fig. 4a, b, respectively. The direction and magnitude of the pooled estimates did not vary considerably for the mortality rate, indicating that the meta-analysis had good reliability. However, the removal of two studies [19, 21] caused the pooled odds ratio for the GOS improvement rate (Fig. 4a) to become insignificant (pooled odds ratio = 4.47, 95 % CI 0.67–29.72, $P = 0.122$ for Rockswold, 2013; pooled odds ratio = 2.18, 95 % CI 0.92–5.17, $P = 0.078$ for Ren et al. [21]), indicating that the meta-analysis had poor reliability.

Publication bias

Publication bias was not assessed because more than 5 studies are required to detect funnel plot asymmetry in the outcomes selected [18].

Quality assessment

All the studies included had randomization and two of them had allocation concealment (Fig. 5). While three of the studies were double-blinded, four of them had blinding of outcome assessment. All the studies had incomplete outcome data and no selective reporting. However, we are not sure if the studies were intention-to-treat analysis. Overall, the included studies had good quality.

Discussion

The clinical significance of hyperbaric oxygen therapy for mild to severe traumatic brain injury remains controversial. Though, HBOT effectively increases the outcomes of TBI and post-concussion syndrome, its benefit to risk ratio in terms of the quality of life is often debated [4, 5, 8, 19]. The present meta-analysis evaluated the effects of HBOT in improving the Glasgow coma scale (GCS) score and symptoms of post-concussion syndrome in patients with mild to severe traumatic brain injury.

Our analysis revealed that improvement in GCS score was significantly higher in the HBOT group than in the control group (Fig. 2). In addition, patients undergoing HBOT achieved a higher rate of improvement in GOS, as compared to the control, normobaric oxygen therapy group. The overall mortality rate was considerably lower in the HBOT group than in the control group. Interestingly, there was no difference among the treatment groups either in the pre-treatment or post-treatment PTSD values. Neither, there was any change in the PTSD score from the baseline in both the groups (Fig. 3).

Our current analysis is in agreement with other studies where hyperbaric oxygen had been shown to increase the GCS score [1, 21], improve [21] and reduce mortality [4]. Though, Bennett et al. [5] have demonstrated an improvement of 2.68 points in GCS with HBOT, they argued that it would not be beneficial in severely impaired TBI patients, where a modest improvement in GCS score would leave the patient in a vegetative, highly dependent stage, adding to the financial burden of the family. On the contrary, Lin et al. have shown that HBOT, apart from improving GCS scores in moderately impaired TBI patients, caused a significant GOS improvement at 6 months in patients with a pre-treatment GOS score of 4 [20]. This delayed effect of HBOT may indicate that even though a noticeable outcome was not seen immediately after HBOT, it is possible to have favorable long-term outcomes later.

The pooled data from our current meta-analysis indicate a 3.13 point difference in the means of the GCS score among the two treatment groups (Fig. 2). While we agree with Bennett et al. [5] that it won't improve the quality of

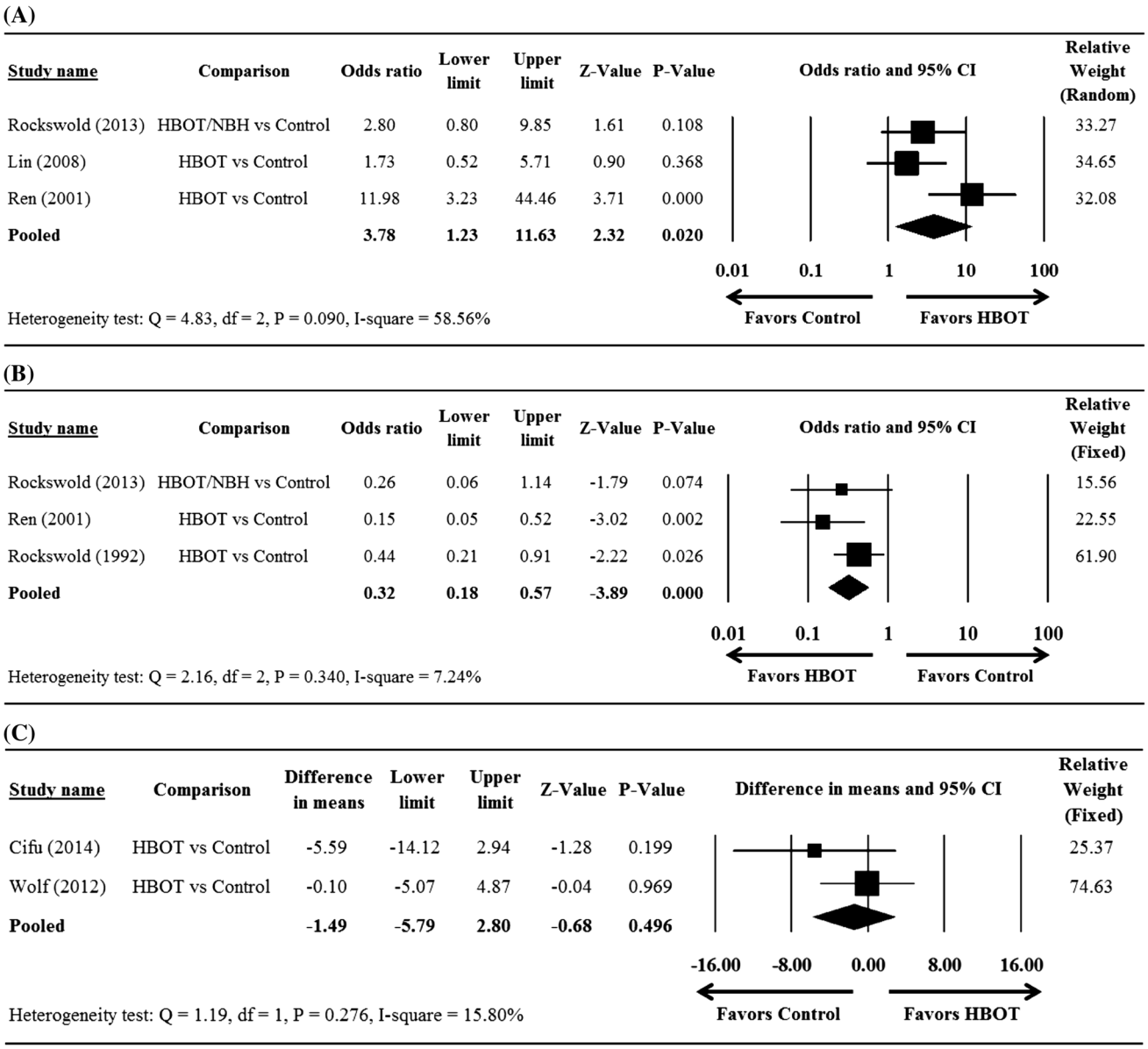

Fig. 3 Forest plots showing results for the meta-analysis of. **a** GOS improved rate, **b** overall mortality rate, and **c** PTSD score change. *CI* confidence interval, *HBOT* hyperbaric oxygen therapy, *NBH* normobaric hyperoxia, *GOS* Glasgow Outcome Score, *PTSD* post-traumatic stress disorder

life of a patient in coma, this data is highly relevant in the treatment of patients with mild TBI, which accounts for 70–90 % of the TBI cases. Moreover, in a crossover study using a treatment protocol of 40 sessions of 60 min each (5 days/week) with 100 % oxygen at 1.5 ATA (atmospheric absolute), HBOT was demonstrated to have significant effects on cognitive function and the quality of life in patients with mild TBI [8].

Even though, the application of HBOT in the treatment of various indications dates back as far as the 1960s, its utility in TBI is fairly recent [6, 9, 22]. Adding to that, the treatment paradigms are not standardized, with variations in atmospheric pressure, length of treatment, and the number of sessions between studies [10, 24]. Meanwhile, studies elsewhere indicate that normobaric oxygen therapy (NBOT) is also equally effective in improving the clinical outcomes, including 6 month GOS and the reduced mortality rate in severe TBI patients [25, 26]. Rockswold et al. [19] have demonstrated a synergistic effect of the combined hyperbaric/normobaric oxygen therapy on cerebral metabolism, intracranial hypertension, overall mortality and GOS at 6 months. The current meta-analysis substantiates the beneficial use of HBOT with good prognosis of consciousness (GCS) and GOS score in patients with mild

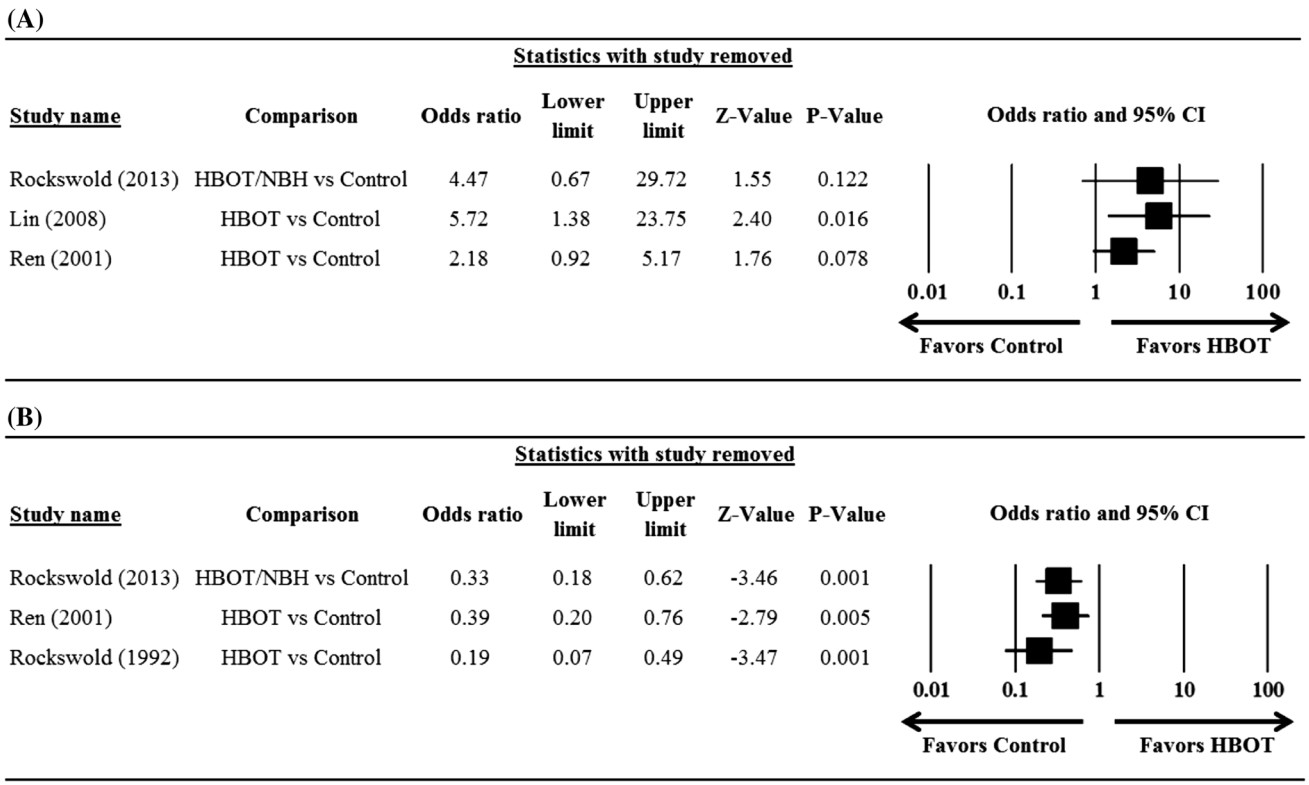

Fig. 4 Sensitivity-analysis for treatment effect of **a** GOS improved rate and **b** overall mortality rate. *CI* confidence interval, *HBOT* hyperbaric oxygen therapy, *NBH* normobaric hyperoxia, *GOS* Glasgow Outcome Score

to severe traumatic brain injury, with post-concussion syndrome. Moreover, HBOT significantly lowered the rate of overall mortality, as compared to the NBOT.

Our findings differ from a recent randomized controlled trial that evaluated the effects of HBOT on symptoms and quality of life among service men ($N = 72$) with persistent percussion syndrome (PCS) [27]. In this multicenter, double-blind, sham-controlled clinical study, Miller et al. compared the safety and efficacy of standard PCS care alone or care supplemented with HBOT. Patients were randomized to one of the three treatment groups: 40 HBOT sessions administered at 1.5 atmospheres absolute (ATA), 40 sham sessions at 1.2 ATA, or no supplemental chamber procedures. Miller et al. that compared with the no intervention group, both groups undergoing supplemental chamber procedures showed improvement on the Rivermead Post-Concussion Symptoms Questionaire (RPQ) ($P \leq 0.02$) but there was not difference between the HBOT and sham groups ($P = 0.70$). Therefore, in service men with persistent PCS, HBOT showed no benefit over sham compression, although they showed improvement compared with PCS care alone. The authors conclude that the findings suggest that the observed improvement is not oxygen mediated but may reflect nonspecific improvements due to placebo effects. It is difficult to compare our findings with this study as different tools were used to assess treatment outcomes and differences in study design between that of Miller et al. and those included in our meta-analysis.

However, there are several limitations to the present analysis. The number of studies included in the final analysis were few even though. More randomized controlled studies with larger cohorts are needed to validate the current results. As mentioned earlier, there is no unanimity in the choice of treatment protocols using HBOT for TBI. Hence, the protocols for HBOT treatment used in the included studies varied widely in their starting time of HBOT, oxygen concentration and the pressure. The mortality data showed good reliability; however, the meta-analysis on GOS had poor reliability. In addition, a subgroup analysis of mild and severe TBI was not performed, due to incomplete reporting of data and the limited number of eligible studies. Whether HBOT has a significantly favorable outcome in mild TBI patients as opposed to severe TBI patients is currently unknown. Long-term studies comparing the efficacy of HBOT in patients with mild vs. severe TBI, with a longer follow-up period should be performed to confirm this. Overall, our results favor the use of HBOT in TBI, especially in patients with mild TBI, the most prevalent form of TBI, where the improvement is

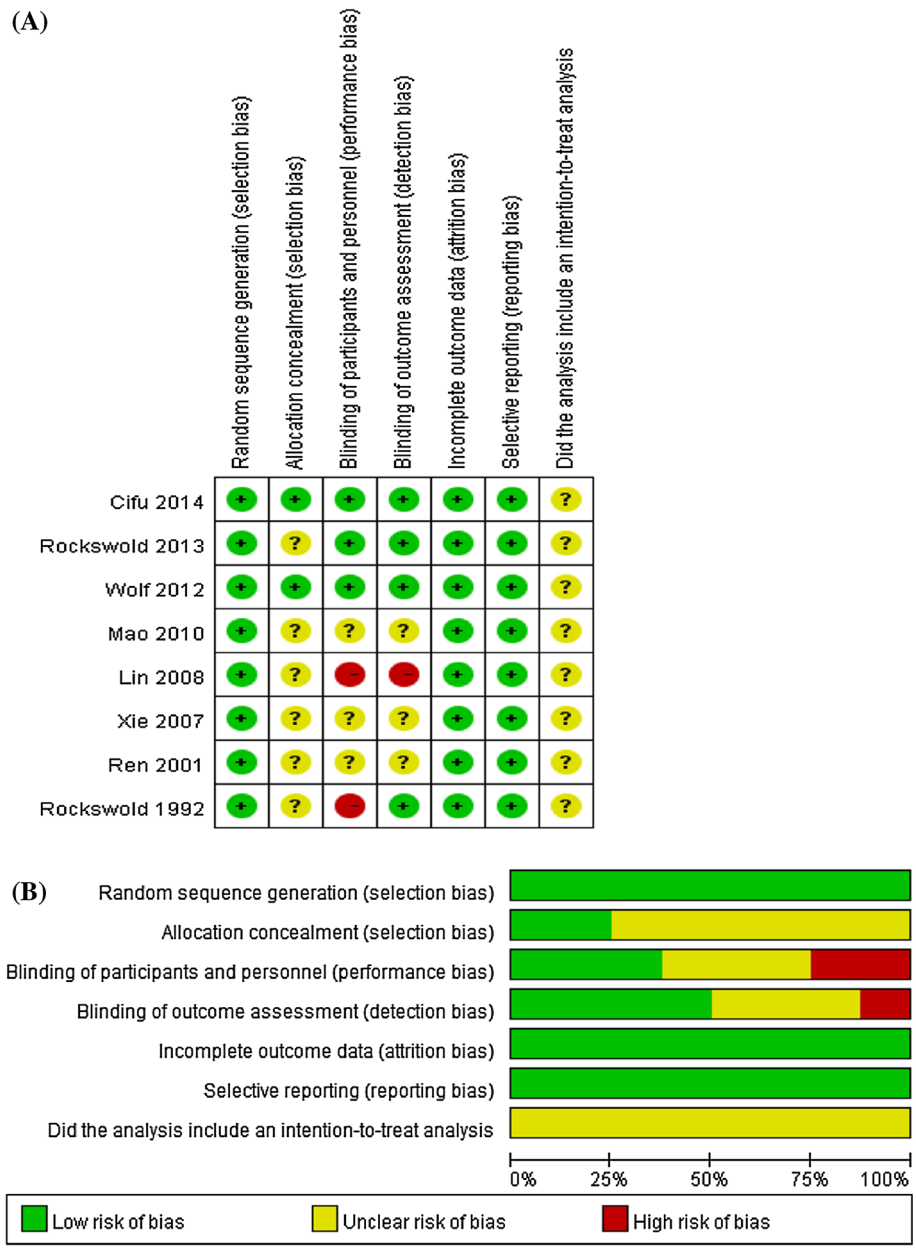

Fig. 5 Quality assessment

highly significant and there is a more general consensus among the studies.

To summarize, the current analysis reveals a higher GCS score, and greater improvement in GOS, and reduced mortality in patients undergoing hyperbaric oxygen therapy. No significant change in the PTSD score was observed. Nevertheless, the favorable outcomes seen in patients undergoing hyperbaric therapy substantiate its utility in the treatment of traumatic brain injury. However, the small number of studies included and the heterogeneity across the studies greatly limits our findings, and points out the need for well-designed studies with similar protocols to investigate the use of HBO therapy in treating traumatic brain injury.

Acknowledgments This study is founded by National Natural Science Foundation of China (No. 81260182); Natural Science Foundation of Yunnan Province (No. 2012FB036).

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

References

1. Xie Z, Zhuang M, Lin L, Xu H, Chen L, Hu L (2007) Changes of plasma C-reactive protein in patients with craniocerebral injury before and after hyperbaric oxygenation: a randomly controlled study. NRR 2(5):314–317
2. Hills BA (1999) A role for oxygen-induced osmosis in hyperbaric oxygen therapy. Med Hypotheses 52(3):259–263

3. Neubauer RA, James P (1998) Cerebral oxygenation and the recoverable brain. Neurol Res 20(Suppl 1):S33–S36
4. Bennett MH, Trytko B, Jonker B (2004) Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. Cochrane Database Syst Rev (4):CD004609
5. Bennett MH, Trytko B, Jonker B (2012) Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. Cochrane Database Syst Rev 12:CD004609
6. Rockswold SB, Rockswold GL, Vargo JM, Erickson CA, Sutton RL, Bergman TA, Biros MH (2001) Effects of hyperbaric oxygenation therapy on cerebral metabolism and intracranial pressure in severely brain injured patients. J Neurosurg 94(3):403–411
7. Golden ZL, Neubauer R, Golden CJ, Greene L, Marsh J, Mleko A (2002) Improvement in cerebral metabolism in chronic brain injury after hyperbaric oxygen therapy. Int J Neurosci 112(2):119–131
8. Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, Friedman M, Hoofien D, Shlamkovitch N, Ben-Jacob E, Efrati S (2013) Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury-randomized prospective trial. PLoS One 8(11):e79995
9. Huang L, Obenaus A (2011) Hyperbaric oxygen therapy for traumatic brain injury. Med Gas Res 1(1):21
10. Wolf G, Cifu D, Baugh L, Carne W, Profenna L (2012) The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. J Neurotrauma 29(17):2606–2612
11. Cifu DX, Hart BB, West SL, Walker W, Carne W (2014) The effect of hyperbaric oxygen on persistent postconcussion symptoms. J Head Trauma Rehabil 29(1):11–20
12. Walker WC, Franke LM, Cifu DX, Hart BB (2013) Randomized, sham-controlled, feasibility trial of hyperbaric oxygen for service members with postconcussion syndrome: cognitive and psychomotor outcomes 1 week postintervention. Neurorehab Neural Re 28(5):420–432
13. Harch PG, Andrews SR, Fogarty EF, Amen D, Pezzullo JC, Lucarini J, Aubrey C, Taylor DV, Staab PK, Van Meter KW (2012) A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. J Neurotrauma 29(1):168–185
14. Rockswold SB, Rockswold GL, Zaun DA, Zhang X, Cerra CE, Bergman TA, Liu J (2010) 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 112(5):1080–1094
15. Murray GD, Teasdale GM, Braakman R, Cohadon F, Dearden M, Iannotti F, Karimi A, Lapierre F, Maas A, Ohman J, Persson L, Servadei F, Stocchetti N, Trojanowski T, Unterberg A (1999) The European Brain Injury Consortium survey of head injuries. Acta Neurochir 141(3):223–236
16. Thurman DJ, Alverson C, Dunn KA, Guerrero J, Sniezek JE (1999) Traumatic brain injury in the USA: A public health perspective. J Head Trauma Rehabil 14(6):602–615
17. Higgins JPL, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods Group; Cochrane Statistical Methods Group (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928
18. Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR (2000) Empirical assessment of effect of publication bias on meta-analyses. BMJ 320(7249):1574–1577 **(PubMed PMID: 10845965)**
19. Rockswold SB, Rockswold GL, Zaun DA, Liu J (2013) 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 118(6):1317–1328
20. Lin JW, Tsai JT, Lee LM, Lin CM, Hung CC, Hung KS, Chen WY, Wei L, Ko CP, Su YK, Chiu WT (2008) Effect of hyperbaric oxygen on patients with traumatic brain injury. Acta neurochirgica Supplement 101:145–149
21. Ren H, Wang W, Ge Z (2001) Glasgow Coma Scale, brain electric activity mapping and Glasgow Outcome Scale after hyperbaric oxygen treatment of severe brain injury. Chin J Traumatol 4(4):239–241
22. Rockswold GL, Ford SE, Anderson DC, Bergman TA, Sherman RE (1992) Results of a prospective randomized trial for treatment of severely brain-injured patients with hyperbaric oxygen. J Neurosurg 76(6):929–934
23. Mao J-H, Sun Z-S, Xiang Y (2010) Observation of curative effects of hyperbaric oxygen for treatment on severe craniocerebral injury. J Clin Neurol 23(5):386–388
24. Davis MC, Shoja MM, Tubbs SR, Griessenauer CJ (2014) Hyperbaric oxygen therapy for chronic post-concussive syndrome. Med Gas Res 4(1):8
25. Kumaria A, Tolias CM (2009) Normobaric hyperoxia therapy for traumatic brain injury and stroke: a review. British J Neurosurg 23(6):576–584
26. Narotam PK, Morrison JF, Nathoo N (2009) Brain tissue oxygen monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. J Neurosurg 111(4):672–682
27. Miller RS, Weaver LK, Bahraini N, Churchill S, Price RC, Skiba V, Caviness J, Mooney S, Hetzell B, Liu J, Deru K, Ricciardi R, Fracisco S, Close NC, Surrett GW, Bartos C, Ryan M, Brenner LA (2015) HOPPS Trial Team. Effects of hyperbaric oxygen on symptoms and quality of life among service members with persistent postconcussion symptoms: a randomized clinical trial. JAMA. Intern Med 175(1):43–52