Adverse Effects of Hyperbaric Oxygen Therapy: a systematic review and meta-analysis

Yu-Yao Zhang
Nanjing Medical University
Yi-Jun Zhou
Nanjing Medical University
Yuan-Yuan Jia
Nanjing Medical University
Tian-Tian Wang
Nanjing Medical University
Dian-Huai Meng (dhdream@126.com)
Jiangsu Province Hospital

Method Article

Keywords: Randomized controlled trial, Systematic review, Meta-analysis, Hyperbaric Oxygen Therapy, Adverse Effects, Safety

Posted Date: January 11th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2453696/v1

Abstract

Objective

Hyperbaric oxygen therapy is one of the common clinical treatments, but adverse effects have hampered and limited the clinical application and promotion of hyperbaric oxygen therapy. We conducted a systematic review and meta-analysis of the adverse effects of hyperbaric oxygen therapy to provide a theoretical basis for clinical treatment.

Methods

Three electronic databases (Pubmed, Web of Science, Cochrane) were comprehensively searched for randomized clinical trials (RCTs) from March, 2012 to October, 2022. Two reviewers independently screened titles and abstracts for eligibility and assessed the quality of the included studies. The meta-analysis was performed using RevMan 5.3.

Results

A total of 26 RCTs involving 1497 participants were identified. HBOT group reported more adverse effects (29.81% vs 10.34%, $P < 0.05$). The most frequent side effect of HBOT is ear discomfort (124 cases). When the courses of hyperbaric oxygen was > 7 sessions, the incidence of adverse effects was higher than that of the control group; when the course of HBOT was ≤ 7 sessions, the adverse effects caused by hyperbaric oxygen were comparatively lower. When chamber pressures are above 2.0 ATA, the incidence of adverse effects is higher than that of the control group; when chamber pressure is below 2.0 ATA, HBOT is relatively safe.

Conclusion

HBOT is more likely to cause adverse reactions when the course of HBOT is > 7 sessions and chamber pressure is above 2.0 ATA.

Introduction

Hyperbaric oxygen therapy (HBOT), a technique through which 100% oxygen is provided at a pressure higher than 1 atm absolute (ATA), has become a well-proven treatment modality for multiple conditions [1]. The clinical application of HBOT is becoming more widespread and currently approved indications include air or gas embolism, acute thermal burn injury, carbon monoxide poisoning, central retinal artery occlusion, clostridial myositis and myonecrosis, decompression sickness, delayed radiation injury, idiopathic sudden sensorineural hearing loss, intracranial abscess, necrotizing soft tissue infections, etc. In addition to approved indications, further studies have demonstrated the potential applications and translation of HBOT in the field of inflammatory and systemic conditions, cancer, COVID-19 and other conditions are summarized[2].

During the application of HBOT, a few adverse effects have been identified, for instance, middle ear barotrauma, sinus and paranasal sinus barotrauma, ocular side effects, hypoglycemia, epilepsy, claustrophobia, etc. [3] The occurrence of these adverse effects affects the application and promotion of HBOT. Systematic reviews and meta-analyses of the adverse effects of HBOT are still lacking. We conducted a systematic review and meta-analysis of the adverse effects of HBOT to provide a theoretical basis for clinical treatment.

Therefore, the research question for this systematic review was:

Does Hyperbaric oxygen therapy cause more adverse effects when compared with sham therapy or another intervention?

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[4] We have registered this review in PROSPERO (registered ID CRD42022316605).

Search Strategy and Selection of Studies:

Three electronic databases (Pubmed, Web of Science, Cochrane) were comprehensively searched for randomized controlled trials (RCTs) from March, 2012 to October, 2022 by two authors independently, with no language restriction. Taking PubMed as an example, the following search terms were used for study retrieval: ((((((((((Hyperbaric Oxygenations) OR (Oxygenations, Hyperbaric)) OR (Hyperbaric Oxygen Therapy)) OR (Hyperbaric Oxygen Therapies)) OR (Oxygen Therapies, Hyperbaric)) OR (Oxygen Therapy, Hyperbaric)) OR (Therapies, Hyperbaric Oxygen)) OR (Therapy, Hyperbaric Oxygen)) OR (Oxygenation, Hyperbaric)) OR (HBO)) OR (HBOT).

1.1 Inclusion And Exclusion Criteria

Only RCTs were included in the analysis. Case-control studies, case series and case reports were not considered. All participants in treatment group received HBOT alone or in combination with other therapeutic approaches, with no restriction on age, gender, race and severity of disease. Patients in control group

received placebo or other treatments except for HBOT. Studies with a retrospective nature, irrelevant topics, no controls, duplicated data or insufficient data were also excluded. The results included the adverse effects of HBOT.

1.2 Methodological Quality And Risk Of Bias Assessment

Two authors evaluated the risk of bias with regard to adverse event outcomes by using the tool recommended by the Cochrane Collaboration Handbook. Each study was categorized into “low”, “unclear” and “high” risk of bias by two reviewers base on following domains: random sequence generation, allocation concealment, blinding to participants, researchers and outcome evaluators, incomplete data, selective outcome reporting and other sources of bias.

1.3 Data Extraction

A pre-defined Excel form was used for data collection. Extracted information included the first author’s name, year of publication, age, sample size, interventions, follow-up and adverse events. We directly contracted the first or correspondence author by e-mail for insufficient or ambiguous data. Discrepancies were resolved by team discussion.

1.4 Statistical Analysis

Statistical analysis was performed by Review Manager 5.3. For each included study, we calculated risk ratio and 95% confidence interval (95% CI) for incidence rate in the intervention arm compared with that of control, based on the reported number of events and sample size. We used the I^2 index to examine heterogeneity across trials for each outcome. A fixed-effect model was utilized for meta-analysis if $I^2 < 25\%$ or $P > 0.10$. Otherwise, a random effect model was used ($I^2 > 25\%$ or $P < 0.10$). Significance was accepted at $P < 0.05$. We conducted subgroup analysis by different control groups, different adverse events, different treatment courses, different chamber pressure, and different types of diseases. For subgroup analysis of different adverse effects, when fewer than two studies report a particular adverse effect, the adverse effect was included in the "other adverse effects"; when the study mentioned the adverse event as a barotrauma but did not mention that the barotrauma site, it was not included in the subgroup analysis. For subgroup analyses of different types of diseases, when there were fewer than two researches studying one disease, the disease was not included in the subgroup analysis.

Results

2.1 Summary of the included studies

Totally 1554 articles were identified. We removed 301 duplications and excluded another 1029 records after screening the title and abstract. Thus, 129 full-text articles were further assessed for eligibility. As shown in Fig. 1, we excluded studies with no reporting of adverse effects(n = 174), only report that no adverse events were reported (n = 18), failure to report exact number of adverse events(n = 6). Finally, 26 RCTs[5–30] involving 1497 participants (842 in HBOT group and 745 in control group) were included for meta-analysis.

Detailed characteristics of included trials were descripted in Table 1. All studies were published from 2012 to 2022. The average age of participants ranged from 5 to 70 years. Hyperbaric oxygen therapy was explicitly described by authors in 14 of the trials, including chamber pressures, treatment courses, and eight of them specify the rate of compression. Diseases involved in the studies includes cerebral palsy, childhood autism, stroke, sudden sensorineural hearing loss, fibromyalgia syndrome, persistent postconcussion symptoms, diabetes with nonhealing ulcers of the lower limb, chronic bowel dysfunction after pelvic radiotherapy, prostate cancer, adhesive postoperative small bowel obstruction, chronic venous leg ulcers, radiation-induced cystitis, osteoradionecrosis, mild traumatic brain injury, central airway stenosis after lung transplantation, COVID- 19 severe hypoxaemia, post-traumatic stress disorder and chronic nonhealing ulcer. In all trials, the treatment course was 7–60 sessions, the chamber pressure in HBOT group was 1.45-2.5ATA, and the chamber pressure in control group was 1.03-2.2ATA. The adverse effects mentioned in the study includes ear discomfort, sinus pain, ocular side effects, seizure, claustrophobia, chest pain, gastrointestinal reaction, headache, fatigue, congestive heart failure.

Table 1
Details of HBOT studies included in the performance meta-analysis

Study ID	Sample size		Age (years)		Disease	Intervention		Course (session
	T	C	T	C		T	C	
Lacey2012[31]	24	22	6.3 ± 1.3	5.2 ± 2.0	Cerebral palsy	100% oxygen at a pressure (or depth) of 1.5ATA	Room Air(21% oxygen) at 1.5ATA	40
Sampanthavivat2012[29]	29	29	6.10	5.67	Childhood autism	100% oxygen at a pressure (or depth) of 1.5ATA	Room Air(21% oxygen) at 1.15ATA	20
Chen2013[5]	33	32	60.3 ± 9.3	60.5 ± 9.5	Progressive cerebral infarction	100% oxygen at a pressure (or depth) of 1.5ATA	Conventional treatment	14
Efrati2013[6]	59	29	61 ± 12	63 ± 6.3	Stroke	90 minutes each, 100% oxygen at 2ATA	Conventional treatment	40
Cvorovic2013[7]	25	25	53.6 ± 15.5	47.3 ± 10.8	Sudden sensorineural hearing loss	100% oxygen at a pressure (or depth) of 2.0ATA	Conventional treatment	20
Efrati2015[8]	48	26	50.4 ± 10.9	48.1 ± 11.1	Fibromyalgia syndrome	90 minutes, 100% oxygen at 2ATA	Conventional treatment	40
Miller2015[9]	24	23	32.5	31.4	Persistent postconcussion symptoms	100% oxygen at a pressure (or depth) of 1.5ATA	Room Air(21% oxygen) at 1.2ATA	40
Fedorko 2016[10]	49	54	61	62	Diabetes with nonhealing ulcers of the lower limb	100% oxygen at a pressure (or depth) of 2.4ATA	Room air (21% oxygen)at 1.2ATA	30
Glover2016[11]	53	28	62.3	62.0	Chronic bowel dysfunction after pelvic radiotherapy	90 minutes, 100% oxygen at 2ATA	Room Air(21% oxygen) at 1.3ATA	40

Study ID	Sample size		Age (years)		Disease	Intervention		Course (sessio
	T	C	T	C		T	C	
Chiles2018[12]	40	43	40–65	40–65	Prostate cancer	100% oxygen at a pressure (or depth) of 2.2ATA	Room Air(21% oxygen) at 2.2ATA	10
Fukami2018[13]	33	40	66	62	Adhesive postoperative small bowel obstruction	100% oxygen at a pressure (or depth) of 2.0ATA	Conservative treatment	7
Santema2017[14]	53	56	67.6	70.6	Ischemic lower extremity ulcers in patients with diabetes	100% oxygen at a pressure (or depth) of 2.4ATA	Standard care	40
Thistlethwaite2018[15]	15	15	70	70	Chronic venous leg ulcers	100% oxygen at a pressure (or depth) of 2.4ATA	Room Air(21% oxygen) at 1.2ATA	30
Oscarsson2019[16]	41	38	64.0	64.8	Radiation-induced cystitis	100% oxygen at a pressure (or depth) of 2.5ATA	Standard care	30–40
Shaw2019[17]	47	53	58.3	58.2	Osteoradionecrosis	100% oxygen at a pressure (or depth) of 2.4ATA	Conventional treatment	30
Weaver2019[18]	60	58	34.8(BIMA)/32.5(HOPPS)	30.8(BIMA)/31.4(HOPPS)	Mild traumatic brain injury	100% oxygen at a pressure (or depth) of 1.5ATA	Room Air(21% oxygen) at 1.2ATA	40
Hadanny2020[19]	30	33	70.68 ± 3.64	68.81 ± 3.34	Healthy older adults	100% oxygen at a pressure (or depth) of 2.0ATA	Conventional treatment	60

Study ID	Sample size		Age (years)		Disease	Intervention		Course (sessio
	T	C	T	C		T	C	
Harch2020[20]	50	27	42.7 ± 10.7	42.3 ± 11.2	Mild traumatic brain injury	100% oxygen at a pressure (or depth) of 1.5ATA	Conventional treatment	40
Schiavo2020[21]	13	11	62 ± 11	61 ± 10	Stroke	100% oxygen at a pressure (or depth) of 2.0ATA	Conventional treatment	40
Curtis2021[22]	17	8	45.7 ± 14.2	51.8 ± 14.5	Fibromyalgia	100% oxygen at a pressure (or depth) of 2.0ATA	Conventional treatment	40
Kraft2021[23]	10	10	59.7	54.5	Central airway stenosis after lung transplantation	100% oxygen at a pressure (or depth) of 2.0ATA	Standard care	20
Cannellotto2022[24]	20	20	52.8 ± 8.5	57.7 ± 9.3	COVID- 19 severe hypoxaemia	100% oxygen at a pressure (or depth) of 1.45ATA	Conventional treatment	7
Doenyas-Barak2022[25]	14	15	39.3 ± 8.1	32.4 ± 9.2	Post-traumatic stress disorder	100% oxygen at a pressure (or depth) of 2.0ATA	Conventional treatment	60
Hadanny2022[26]	15	10	11.99 ± 2.32	11.00 ± 2.32	Post-concussion syndrome	100% oxygen at a pressure (or depth) of 1.5ATA	Room Air(21% oxygen) at 1.03ATA	60
Wolf2018[27]	25	25	28.3 ± 8.1	28.4 ± 7.4	Traumatic Brain Injury	100% oxygen at a pressure (or depth) of 2.4ATA	Room Air(21% oxygen) at 1.3ATA	30
Kaur2012[28]	15	15	46.9 ± 11.8	47.4 ± 12.5	Chronic nonhealing ulcer	100% oxygen at a pressure (or depth) of 2.5ATA	conventional treatment	30

2.2 Meta-analysis Results

2.2.1 Incidence of adverse effects

There was a heterogeneity between studies(P = 0.06,I^2 = 33%), therefore a random-effect model was performed. The results indicated that the incidence of AEs in HBOT group was higher than that in control group (29.81% vs 10.34%, RR = 2.88,95%CI: 1.78–3.32,P < 0.05;Figure 3).

2.2.2 Subgroup Analysis

2.2.2.1 Effect of different control groups

In eight studies, participants in control group received sham therapy. Compared with patients in control group, patients in HBOT group were more likely to have AEs (43.11 22.47 RR = 1.92,95%CI: 1.13–2.55, P = 0.01; Fig. 4), with high heterogeneity (P = 0.010,I^2 = 68%).In fifteen studies, patients in control group received conventional treatment. The results indicated that the incidence of AEs was higher in HBOT than in the control group(21.06 2.740RR = 7.69,95%CI 2.56–7.61, P 0.00001; Fig. 4), with low heterogeneity(P = 0.38,I^2 = 7%).

2.2.2.2 Effect Of Different Adverse Events

Table 2 summarizes the results of subgroup analysis of different adverse events. We found significantly increased risk ratios with HBOT compared to control group for two specific adverse events: ear discomfort, and ocular side effects.

1. Ear discomfort: Twenty-four studies[5–7, 9-22, 24–29,31]reported ear discomfort. The risk of ear discomfort was increased in participants treated with HBOT compared to neither sham therapy nor other conventional treatment(RR = 3.30,95%CI: 1.96–3.70,P 0.01),with moderate heterogeneity(P = 0.15,I^2 = 23%).
2. Sinus pain: Three studies[9,17,18]reported sinus pain. The incidence of sinus pain was higher in HBOT than in the control group, with low heterogeneity(P = 0.28,I^2 = 21%). The difference was not statistically significant(RR = 0.88,95%CI: 0.32–2.29,P > 0.05).
3. Ocular side effects: Nine studies[9–12, 16-19,22]reported ocular side effects. The risk of ocular side effects was increased in participants treated with HBOT compared to neither sham therapy nor other conventional treatment(RR = 2.37,95%CI: 1.29–3.32,P 0.05),with no heterogeneity(P = 0.83,I^2 = 0%).
4. Seizure: Two studies[14,17]reported seizure. The incidence of seizure was higher in HBOT than in the control group, with no heterogeneity(P = 0.98,I^2 = 0%). The difference was not statistically significant(95%CI: 0.35–30.92,P > 0.05).
5. Claustrophobia: Three studies[9,23,28]reported claustrophobia. The incidence of claustrophobia was higher in HBOT than in the control group, with no heterogeneity(P = 0.42,I^2 = 0%). The difference was not statistically significant(RR = 2.94,95%CI: 0.40–7.94,P > 0.05).
6. Chest pain: Three studies[10,17,21]reported chest pain. The incidence of chest pain was higher in HBOT than in the control group, with no heterogeneity(P = 0.94,I^2 = 0%). The difference was not statistically significant(95%CI: 0.64–22.13,P > 0.05).
7. Gastrointestinal reaction: Two studies[5,10]reported gastrointestinal reaction. The incidence of gastrointestinal reaction was higher in HBOT than in the control group, with no heterogeneity(P = 0.95,I^2 = 0%). The difference was not statistically significant(RR = 4.22,95%CI: 0.15–19.60,P > 0.05).
8. Headache: Four studies[9,18,26,28]reported headache. The incidence of headache was lower in HBOT than in the control group, with no heterogeneity(P = 0.70,I^2 = 0%). The difference was not statistically significant(RR = 1.86,95%CI: 0.46–5.28,P > 0.05).
9. Fatigue: Three studies[11,17,20]reported fatigue. The incidence of chest pain was higher in HBOT than in the control group, with no heterogeneity(P = 0.31,I^2 = 15%). The difference was not statistically significant(RR = 1.20,95%CI 0.29–3.10,P > 0.05).
10. Congestive heart failure: Two studies[10,16]reported congestive heart failure. The incidence of congestive heart failure was higher in HBOT than in the control group, with no heterogeneity(P = 0.30,I^2 = 6%). The difference was not statistically significant(RR = 1.02,95%CI:0.15–6.77,P > 0.05).
11. Other AEs: Other AEs caused by HBOT included hypoglycemia, vertigo, tooth pain, somnolence, anxiety, dyspnea, hyperventilation, urinary incontinence, urinary tract infection, hypotension, and hypertension, as shown in Table 3.

Table 2
Results of subgroup analysis of different adverse events

Adverse events	No. of trails	P	RR	95%CI	Test of Heterogeneity	
					P	I^2%
ear discomfort	24	0.01	3.30	1.96–3.70	0.15	23
sinus pain	3	0.77	0.88	0.32–2.29	0.28	21
ocular side effects	9	0.01	2.37	1.29–3.32	0.83	0
seizure	2	0.30	—*	0.35–30.92	0.98	0
claustrophobia	3	0.45	2.94	0.40–7.94	0.42	0
chest pain	3	0.14	—*	0.64–22.13	0.94	0
gastrointestinal reaction	2	0.21	4.22	0.15–19.60	0.95	0
headache	4	0.47	1.86	0.46–5.28	0.70	0
fatigue	3	0.92	1.20	0.29–3.10	0.31	15
congestive heart failure	2	0.99	1.02	0.15–6.77	0.30	6

"*": the incidence of this adverse effect in the control group was 0. The relative risk could not be calculated. 5.26 2.83

Table 3
Other adverse events during HBOT

Adverse events	Study ID	HBOT		Control	
		events	total	events	total
Hypoglycemia	Fedorko2016[10]	4	49	1	54
Dizziness/ vertigo	Weaver2019[18]	2	60	2	58
Tooth pain	Miller2015[9]	1	24	0	23
Somnolent	Weaver2019[18]	1	60	1	58
Anxiety	Weaver2019[18]	1	60	0	58
Dyspnea	Weaver2019[18]	2	60	0	58
Hyperventilation	Weaver2019[18]	1	60	0	58
Incontinence	Chiles2018[12]	2	40	0	43
Urinary tract infection	Chiles2018[12]	1	40	0	43
Meatal stenosis	Chiles2018[12]	0	40	1	43
Hypotension	Shaw2019[17]	1	47	0	53
Hypertension	Chiles2018[12]	1	40	0	43

2.2.2.3effect Of Different Treatment Courses

In two studies, participants in HBOT group received ≤ 7 sessions HBOT. The incidence of AEs was higher in HBOT than in the control group, with no heterogeneity(P = 0.93,I^2 = 0%). The difference was not statistically significant (95%CI:0.35–30.65, $P > 0.05$). In five studies, participants in HBOT group received 8–20 sessions HBOT. Compared with patients in control group, patients in HBOT group were more likely to have AEs (RR = 4.06,95%CI:1.60–7.89, P = 0.002), with no heterogeneity(P = 0.97,I^2 = 0%). In nineteen studies, patients in HBOT group received 20 sessions HBOT. Compared with patients in control group, patients in HBOT group were more likely to have AEs (RR = 2.51,95%CI:1.63–4.33, P 0.05;Figure 5) ,with high heterogeneity(P 0.00001,I^2 = 75%).

2.2.2.4 Effect Of Different Chamber Pressure

The studies were divided into two subgroups according to chamber pressure. The result demonstrated heterogeneity in the subgroup with chamber pressures ≥ 2.0ATA (P = 0.11, I^2 = 34%), which was therefore analyzed using a random-effects model. Due to the high chamber pressure in some of the control groups, the studies with sham therapy control groups were not included in this subgroup analysis. The incidence of adverse effects was higher in HBOT group than in control group for subgroups with chamber pressure ≥ 2.0 ATA, with statistically significant differences in the results (RR = 7.99,95%CI:3.03–14.96,

P 0.0001;Figure 6). The difference in the incidence of adverse effects between the hyperbaric and control groups in the subgroup with pressure < 2.0 ATA was not statistically significant (R = 5.40,95% CI: 0.59–13.84, P > 0.05; Fig. 6).

2.2.2.5 Effect Of Different Types Of Diseases

The studies were divided into traumatic brain injury subgroup, stroke subgroup, and diabetic foot subgroup. Adverse effects were more frequent in HBOT group than in control group in the diabetic foot subgroup (Fig. 7).

Discussion

The results of this meta-analysis demonstrated that the incidence of adverse effects was higher in the hyperbaric group than the control group. The main adverse effects of HBOT include ear discomfort (e.g., middle ear barotrauma, ear pain, etc.), ocular side effects (e.g., myopia, hyperopia, etc.), sinus barotrauma, epilepsy, claustrophobia, chest pain, headache, fatigue, gastrointestinal reactions, etc. Most adverse effects of hyperbaric oxygen are mild and self-limiting, the most common of which is middle ear barotrauma, an adverse effect that can be prevented by ongoing teaching of middle ear clearing techniques and appropriate compression rates [3].

The results of this meta-analysis revealed that the incidence of adverse effects was higher in HBOT group than in control group, regardless of whether the control group was a sham or conventional treatment group. The adverse effects of HBOT can be divided into two categories: adverse effects of pressure and adverse effects of oxygen. The adverse effect of pressure is barotrauma, which can affect any closed, air-filled cavity (including but not limited to ears, sinus, teeth, lungs, and bowel). The adverse effects of oxygen can further be subdivided into three categories: pulmonary, neurologic, and ophthalmologic [32]. Patients in the sham therapy group were mostly treated with normobaric or hyperbaric room air. In Chiles2018[12] and Lacey2012[31], chamber pressures in control groups were consistent with that of the HBOT groups. The incidence of ear discomfort in these studies was found to be similar in the HBOT groups (14.06%) to the control groups (13.85%). Therefore, the factor of injury for ear discomfort may originate more from pressure rather than oxygen toxicity.

Both ear and ocular adverse effects were more frequent in HBOT than in the control group, while the differences in the incidence of the remaining several adverse effects were not statistically significant. It might be due to several reasons: the exclusion of this adverse effect as a contraindication; the small number of cases involving this adverse effect; and the relatively mild clinical manifestation of the adverse effect, which failed to attract the attention of the participants.

Data analysis indicated that a lower incidence of claustrophobia was found in the HBOT group than in the control group. There is a possibility that this is due to the fact that the control group in Miller2015[9] was a sham therapy group in which participants would also enter the chamber; in parallel, claustrophobia is one of the contraindications to HBOT and few people have previous claustrophobia that is not detected. Claustrophobia may be managed with coaching and anxiolytic medications. Intolerance of a monoplace chamber may warrant referral to the closest multiplace chamber facility[3].

Some adverse effects may also be related to the patient's health condition, for instance participants in Chiles2018[12] experienced adverse effects in the form of urinary incontinence and urinary tract infections, which may be related to undergoing radical prostate cancer surgery. Likewise, cardiovascular adverse effects show a similar pattern. The onset of congestive heart failure in the patients of Fedorko2016[10] and Oscarsson2019[16] in this study may also be associated with the participants' health conditions. With regard to the mechanisms of congestive heart failure, a study by Weaver et al. [33] suggested that hyperbaric oxygen therapy could increase left ventricular (LV) afterload, increase LV filling pressures, increase oxidative myocardial stress, decrease LV compliance by oxygen radical-mediated reduction in nitric oxide, alter cardiac output between the right and left hearts, and induce bradycardia with concomitant LV dysfunction. Therefore, caution should be exercised in the use of hyperbaric oxygen therapy in patients with heart failure or in patients with reduced cardiac ejection fractions. As regards the effect of HBOT on blood pressure, most researches report an increase in blood pressure. Al-Waili et al.[34] pointed out that hyperbaric oxygen can cause hypertension, which was seen in one case of hypertension in the hyperbaric group in Chiles2018 [12]. A different result, however, was seen in Shaw 2019[17], where there was one case of hypotension, but the study did not mention its cause.

Our results revealed that at a course of > 7 sessions, the incidence of adverse effects was greater than that of the control group. When the treatment course was ≤ 7 sessions, the adverse effects were relatively low. The main adverse effects that warranted attention were ear adverse effects, such as ear pain [13,24]. The outcome implies that the course of HBOT is a major influencing factor for the adverse effects, hence we recommend that the course of hyperbaric oxygen treatment should be shortened to less than 7 sessions to reduce the occurrence of side effects.

In the present study, the results indicated that patients received HBOT at chamber pressures above 2.0 ATA had a higher incidence of adverse effects than the control group. The incidence of adverse effects is relatively low with a chamber pressure below 2.0 ATA. The adverse effects to be cautioned about are mainly ear discomfort, ocular side effects, headache, sinus barotrauma, etc. [5,9,18,20,24,31] Ajayi et al. [35] suggested that the incidence of adverse effects of HBOT at a chamber pressure of 2.0 ATA was similar to that of 2.4 ATA. As for the incidence of epilepsy, Marvin et al. [36]noted there was a statistically significant difference for seizure between the different pressures. They also demonstrated a statistically significant increased risk of seizure with increasing treatment pressure. Research by Resanovic et al. and Mijajlovicl et al [37,38], however, suggested that HBOT with chamber pressures below 3.0 ATA rarely caused adverse effects. It is probably related to the fact that in general the adverse effects of HBOT are mild and mostly self-limiting [3] ,as such many patients do not report even though the adverse effect occur.

It has also been suggested that the incidence of adverse effects related to different time interval and rate (slope) of compression [39]. Nevertheless, subgroup analyses were not performed since fewer of the studies explicitly described time interval and rate of compression and did not include them as a categorical or

control factor, which may affect the accuracy of the data analysis. Eight of the included studies[5,7,12,13,15,19,27,31] specify the rate of compression, but valid data statistics could not be performed as the rate of compression in the control group was not mentioned. Also, ten studies [10–12, 15,19–22, 25,27] reported time intervals. Owing to the 5-minute time interval in most of the studies and the 0-minute interval in only one study, however, it was infeasible to group the studies for subgroup analysis.

The results of this study revealed that the incidence of adverse effects was higher in patients with diabetic foot when received HBOT. Particular attention is needed to the hypoglycemic occurrence in diabetics received HBOT. It has been documented that in diabetics undergoing HBO_2, severe hypoglycemia is rare and occurs more frequently in Type 1 diabetes. Pre-HBO_2 glucose values may be used to predict subsequent hypoglycemia and reduce the need for routine glucose monitoring during and after HBOT [40]. Fedorko2016[10], a study of diabetes with nonhealing ulcers of the lower limb, saw an occurrence of hypoglycemia in four of the sixty-one patients in the HBOT group.

Limitations also exist in this study. The small number of cases of partial adverse effects during subgroup analysis may have an implication on the results of the data analysis, especially when the heterogeneity between these small number of studies is relatively high. Exclusion as a contraindication resulted in a significant reduction in the incidence of some adverse reactions, as in claustrophobia, leading to no statistical significance of the difference in the incidence of this adverse effect between the HBOT and control groups.

In conclusion, the main adverse effects of HBOT include ear discomfort (e.g., middle ear barotrauma, ear pain, etc.), ocular side effects (e.g., myopia, hyperopia, etc.), sinus barotrauma, epilepsy, claustrophobia, chest pain, headache, fatigue, and gastrointestinal reactions. HBOT is more likely to cause adverse reactions when the treatment course of hyperbaric oxygen is > 7 sessions and chamber pressure is above 2.0 ATA.

Declarations

Ethics approval: Not applicable.

Competing interests: Nil.

Source(s) of support: Key R&D Program of Jiangsu Province (grant No. BE2021012-4).

Acknowledgements:

Correspondence: Dian-Huai Meng, Rehabilitation Medicine Center, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China, Email dhdream@126.com.

References

1. Fu Q, Duan R, Sun Y, Li Q. Hyperbaric oxygen therapy for healthy aging: From mechanisms to therapeutics. Redox Biol. 2022;53:102352.
2. Ortega MA, Fraile-Martinez O, Garcia-Montero C et al. A General Overview on the Hyperbaric Oxygen Therapy: Applications, Mechanisms and Translational Opportunities.Medicina (Kaunas). 2021;57(9).
3. Heyboer M 3rd, Sharma D, Santiago W, McCulloch N. Hyperbaric Oxygen Therapy: Side Effects Defined and Quantified. Adv Wound Care (New Rochelle). 2017;6(6):210–24.
4. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1–34.
5. Chen FP, Yu XX. Short-term effect of hyperbaric oxygen combined with edaravone and ozagrel sodium in treating progressive cerebral infarction. Chin J evidence-based Med. 2013;13(4):413–6.
6. Efrati S, Fishlev G, Bechor Y et al. Hyperbaric Oxygen Induces Late Neuroplasticity in Post Stroke Patients - Randomized, Prospective Trial.Plos One.2013;8(1).
7. Cvorovic L, Jovanovic MB, Milutinovic Z, Arsovic N, Djeric D. Randomized prospective trial of hyperbaric oxygen therapy and intratympanic steroid injection as salvage treatment of sudden sensorineural hearing loss. Otol Neurotol. 2013;34(6):1021–6.
8. Efrati S, Golan H, Bechor Y et al. Hyperbaric Oxygen Therapy Can Diminish Fibromyalgia Syndrome - Prospective Clinical Trial.Plos One.2015;10(5).
9. Miller RS, Weaver LK, Bahraini N, et al. Effects of Hyperbaric Oxygen on Symptoms and Quality of Life Among Service Members With Persistent Postconcussion Symptoms A Randomized Clinical Trial. Jama Intern Med. 2015;175(1):43–52.
10. Fedorko L, Bowen JM, Jones W, et al. Hyperbaric Oxygen Therapy Does Not Reduce Indications for Amputation in Patients With Diabetes With Nonhealing Ulcers of the Lower Limb: A Prospective, Double-Blind, Randomized Controlled Clinical Trial. Diabetes Care. 2016;39(3):392–9.
11. Glover M, Smerdon GR, Andreyev HJ, et al. Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (HOT2): a randomised, double-blind, sham-controlled phase 3 trial. Lancet Oncol. 2016;17(2):224–33.
12. Chiles KA, Staff I, Johnson-Arbor K, Champagne A, McLaughlin T, Graydon RJ. A Double-Blind, Randomized Trial on the Efficacy and Safety of Hyperbaric Oxygenation Therapy in the Preservation of Erectile Function after Radical Prostatectomy. J Urol. 2018;199(3):805–11.
13. Fukami Y, Kobayashi S, Sekoguchi E, Kurumiya Y. Randomized controlled trial of hyperbaric oxygen therapy in adhesive postoperative small bowel obstruction. Langenbecks Arch Surg. 2018;403(5):555–9.

14. Santema KTB, Stoekenbroek RM, Koelemay MJW, et al. Hyperbaric Oxygen Therapy in the Treatment of Ischemic Lower- Extremity Ulcers in Patients With Diabetes: Results of the DAMO(2)CLES Multicenter Randomized Clinical Trial. Diabetes Care. 2018;41(1):112–9.
15. Thistlethwaite KR, Finlayson KJ, Cooper PD, et al. The effectiveness of hyperbaric oxygen therapy for healing chronic venous leg ulcers: A randomized, double-blind, placebo-controlled trial. Wound Repair Regen. 2018;26(4):324–31.
16. Oscarsson N, Muller B, Rosen A, et al. Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): a randomised, controlled, phase 2–3 trial. Lancet Oncol. 2019;20(11):1602–14.
17. Shaw RJ, Butterworth CJ, Silcocks P, et al. HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): A Randomized Controlled Trial of Hyperbaric Oxygen to Prevent Osteoradionecrosis of the Irradiated Mandible After Dentoalveolar Surgery. Int J Radiat Oncol Biol Phys. 2019;104(3):530–9.
18. Weaver LK, Churchill S, Wilson SH, Hebert D, Deru K, Lindblad AS. A composite outcome for mild traumatic brain injury in trials of hyperbaric oxygen. Undersea Hyperb Med. 2019;46(3):341–52.
19. Hadanny A, Daniel-Kotovsky M, Suzin G, et al. Cognitive enhancement of healthy older adults using hyperbaric oxygen: a randomized controlled trial. Aging (Albany NY). 2020;12(13):13740–61.
20. Harch PG, Andrews SR, Rowe CJ, et al. Hyperbaric oxygen therapy for mild traumatic brain injury persistent postconcussion syndrome: a randomized controlled trial. Med Gas Res. 2020;10(1):8–20.
21. Schiavo S, Richardson D, Santa Mina D, et al. Hyperbaric oxygen and focused rehabilitation program: a feasibility study in improving upper limb motor function after stroke. Appl Physiol Nutr Metab. 2020;45(12):1345–52.
22. Curtis K, Katz J, Djaiani C, et al. Evaluation of a Hyperbaric Oxygen Therapy Intervention in Individuals with Fibromyalgia. Pain Med. 2021;22(6):1324–32.
23. Kraft BD, Mahmood K, Harlan NP, et al. Hyperbaric oxygen therapy to prevent central airway stenosis after lung transplantation. J Heart Lung Transplant. 2021;40(4):269–78.
24. Cannellotto M, Duarte M, Keller G, et al. Hyperbaric oxygen as an adjuvant treatment for patients with COVID-19 severe hypoxaemia: a randomised controlled trial. Emerg Med J. 2022;39(2):88–93.
25. Doenyas-Barak K, Catalogna M, Kutz I, et al. Hyperbaric oxygen therapy improves symptoms, brain's microstructure and functionality in veterans with treatment resistant post-traumatic stress disorder: A prospective, randomized, controlled trial. PloS one. 2022;17(2):e0264161–1.
26. Hadanny A, Catalogna M, Yaniv S, et al. Hyperbaric oxygen therapy in children with post-concussion syndrome improves cognitive and behavioral function: a randomized controlled trial. Sci Rep. 2022;12(1):15233–3.
27. Nct. Treatment of Traumatic Brain Injury With Hyperbaric Oxygen Therapy. i>https://clinicaltrialsgov/show/NCT00810615. 2008.
28. Kaur S, Pawar M, Banerjee N, Garg R. Evaluation of the efficacy of hyperbaric oxygen therapy in the management of chronic nonhealing ulcer and role of periwound transcutaneous oximetry as a predictor of wound healing response: A randomized prospective controlled trial. J Anaesthesiol Clin Pharmacol. 2012;28(1):70–5.
29. Sampanthavivat M, Singkhwa W, Chaiyakul T, Karoonyawanich S, Ajpru H. Hyperbaric oxygen in the treatment of childhood autism: a randomised controlled trial. Diving Hyperb Med. 2012;42(3):128–33.
30. !!!. INVALID CITATION !!!.
31. Lacey DJ, Stolfi A, Pilati LE. Effects of hyperbaric oxygen on motor function in children with cerebral palsy. Ann Neurol. 2012;72(5):695–703.
32. Sadri RA, Cooper JS. Hyperbaric Complications. In:StatPearls.Treasure Island (FL)2022.
33. Weaver LK, Churchill S. Pulmonary edema associated with hyperbaric oxygen therapy. Chest. 2001;120(4):1407–9.
34. Al-Waili NS, Butler GJ, Beale J, et al. Influences of hyperbaric oxygen on blood pressure, heart rate and blood glucose levels in patients with diabetes mellitus and hypertension. Archives of Medical Research. 2006;37(8):991–7.
35. Ajayi OD, Gaskill Z, Kelly M, Logue CJ, Hendricksen SM. A comparison of two hyperbaric oxygen regimens: 2.0 ATA for 120 minutes to 2.4 ATA for 90 minutes in treating radiation-induced cystitis Are these regimens equivalent? Undersea Hyperb Med. 2020;47(4):581–9.
36. Heyboer M 3rd, Jennings S, Grant WD, Ojevwe C, Byrne J, Wojcik SM. Seizure incidence by treatment pressure in patients undergoing hyperbaric oxygen therapy. Undersea Hyperb Med. 2014;41(5):379–85.
37. Resanovic I, Zaric B, Radovanovic J, et al. Hyperbaric Oxygen Therapy and Vascular Complications in Diabetes Mellitus. Angiology. 2020;71(10):876–85.
38. Mijajlovic MD, Aleksic V, Milosevic N, Bornstein NM. Hyperbaric oxygen therapy in acute stroke: is it time for Justitia to open her eyes? Neurol Sci. 2020;41(6):1381–90.
39. O'Neill OJ, Dayya D, Varughese L, Marker JA, Perez L, Dayya M. The effect of total compression time and rate (slope) of compression on the incidence of symptomatic Eustachian tube dysfunction and middle ear barotrauma: a Phase II prospective study. Undersea Hyperb Med. 2021;48(3):209–19.
40. Stevens SL, Narr AJ, Claus PL, et al. The incidence of hypoglycemia during HBO2 therapy: A retrospective review. Undersea Hyperb Med. 2015;42(3):191–6.

Figures

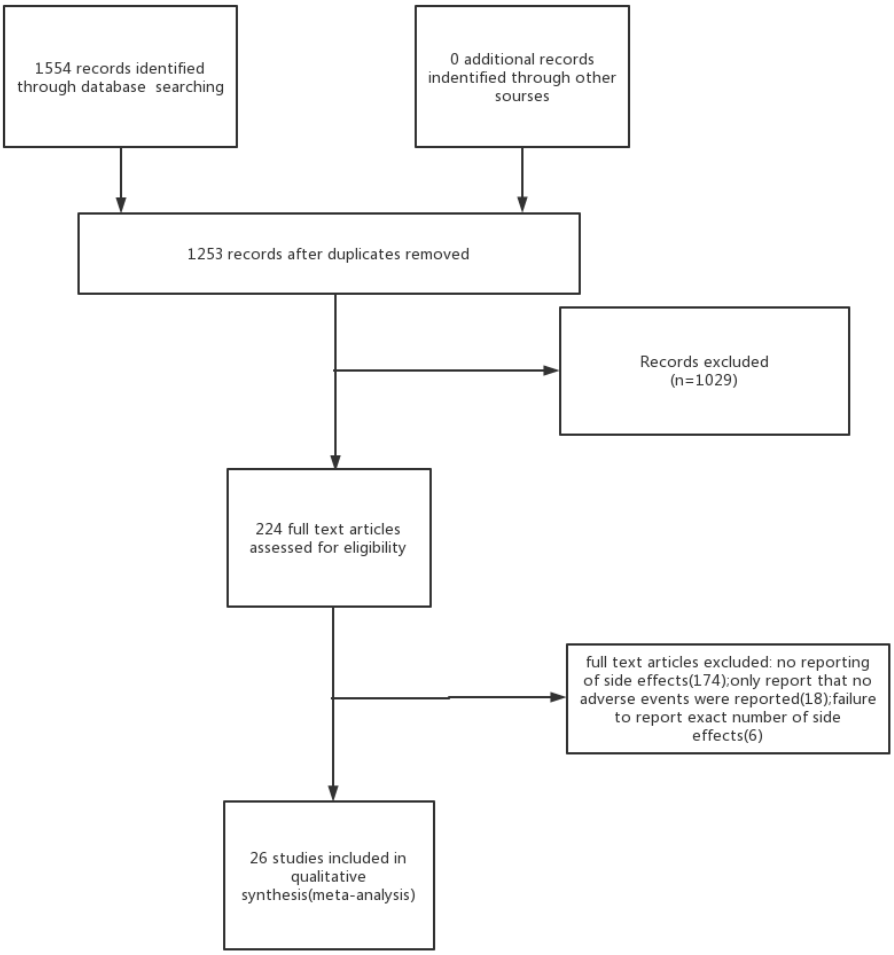

Figure 1

Study selection.

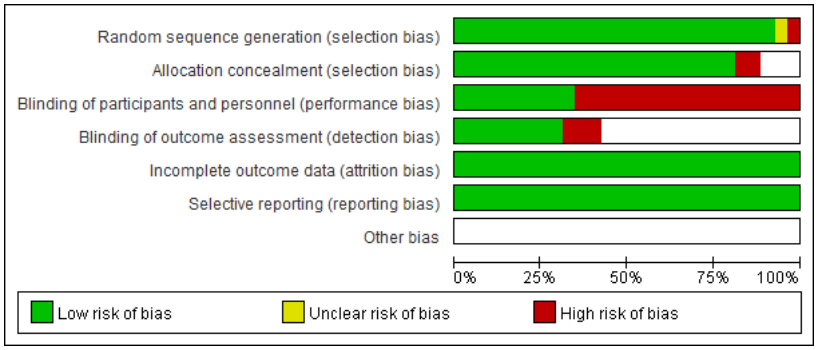

Figure 2

Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

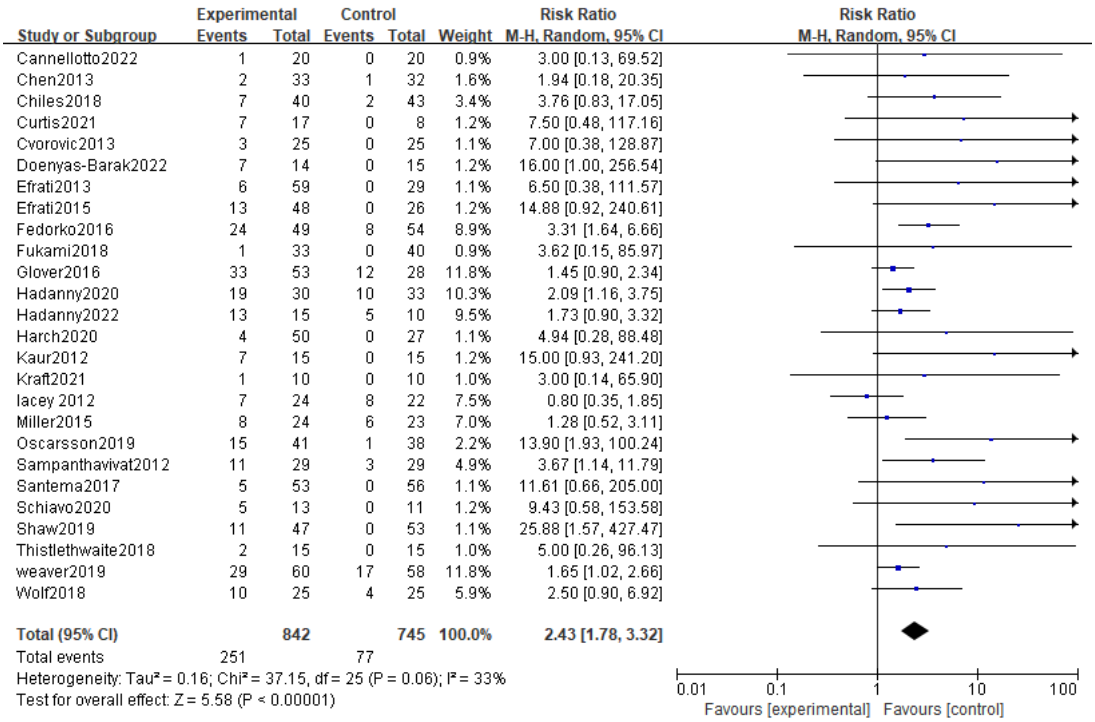

Figure 3

Analysis 1.1: HBOT versus any control group, any adverse event.CI: confidence intervaldf: degrees of freedom M-H: Mantel-Haenszel method of meta-analysis P: probability Z: Z score (standard score)

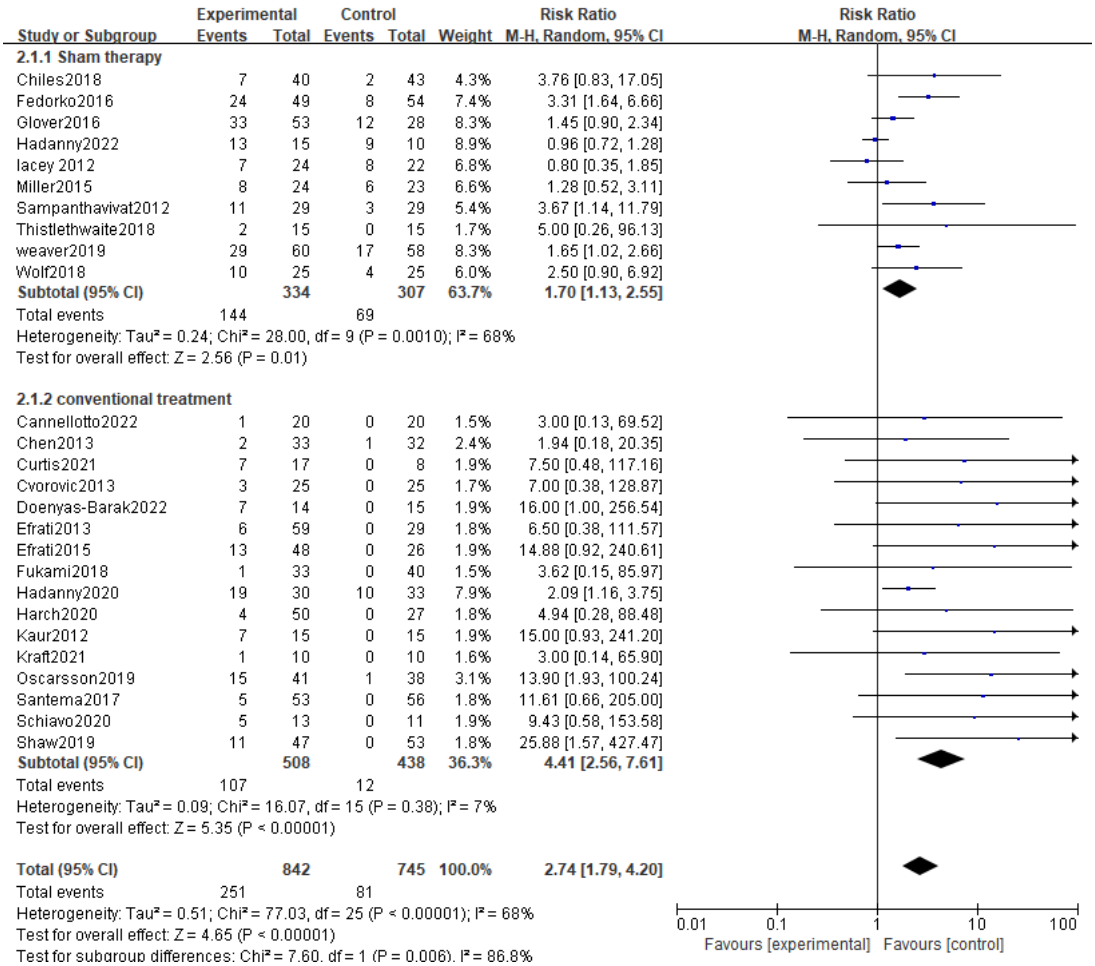

Figure 4

Analysis 2.1: HBOT versus sham therapy and conventional treatment, any adverse event.CI: confidence intervaldf: degrees of freedom M-H: Mantel-Haenszel method of meta-analysis P: probability Z: Z score (standard score)

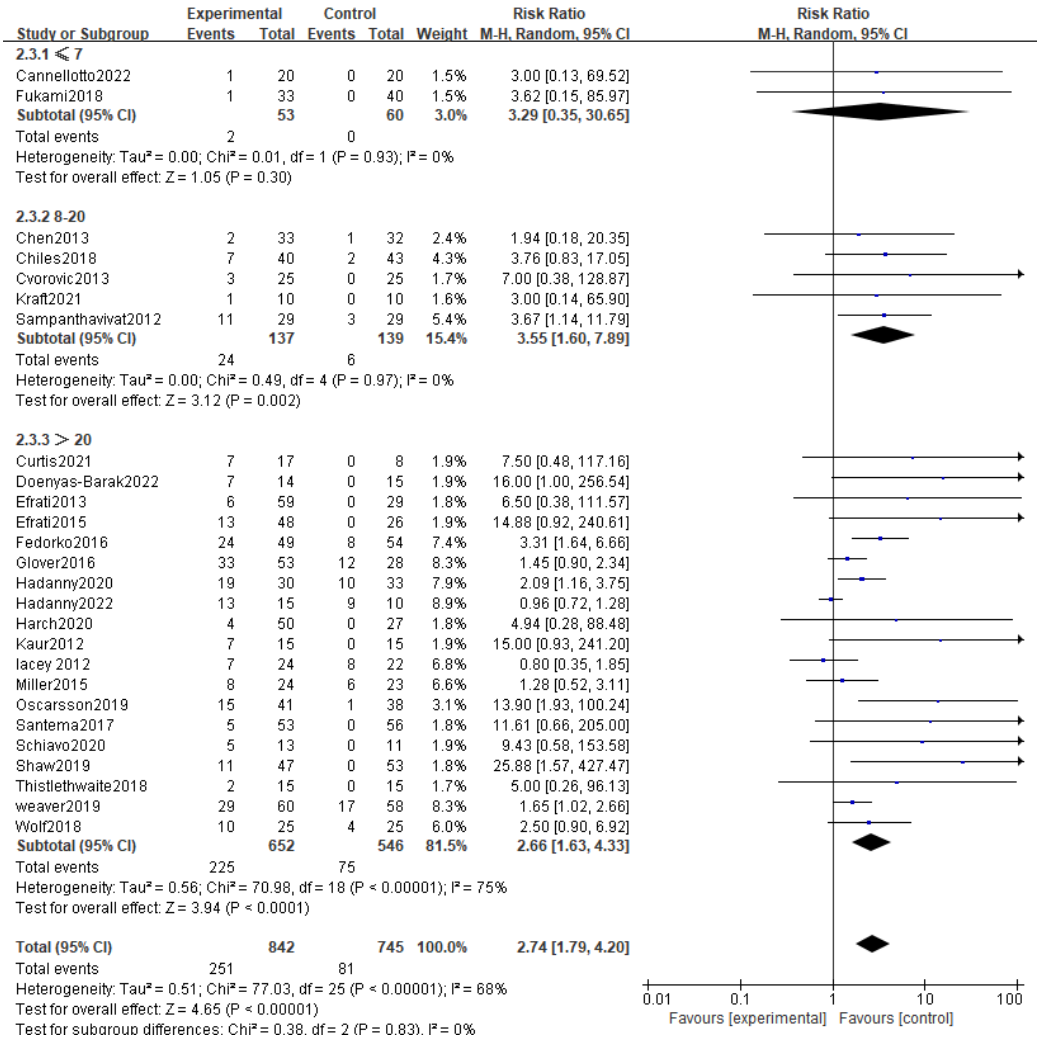

Figure 5

Analysis 2.3: ≤ 7 sessions ,8-20 sessions, 20 sessions of HBOT versus any control group, any adverse event.CI: confidence intervaldf: degrees of freedom M-H: Mantel-Haenszel method of meta-analysis P: probability Z: Z score (standard score)

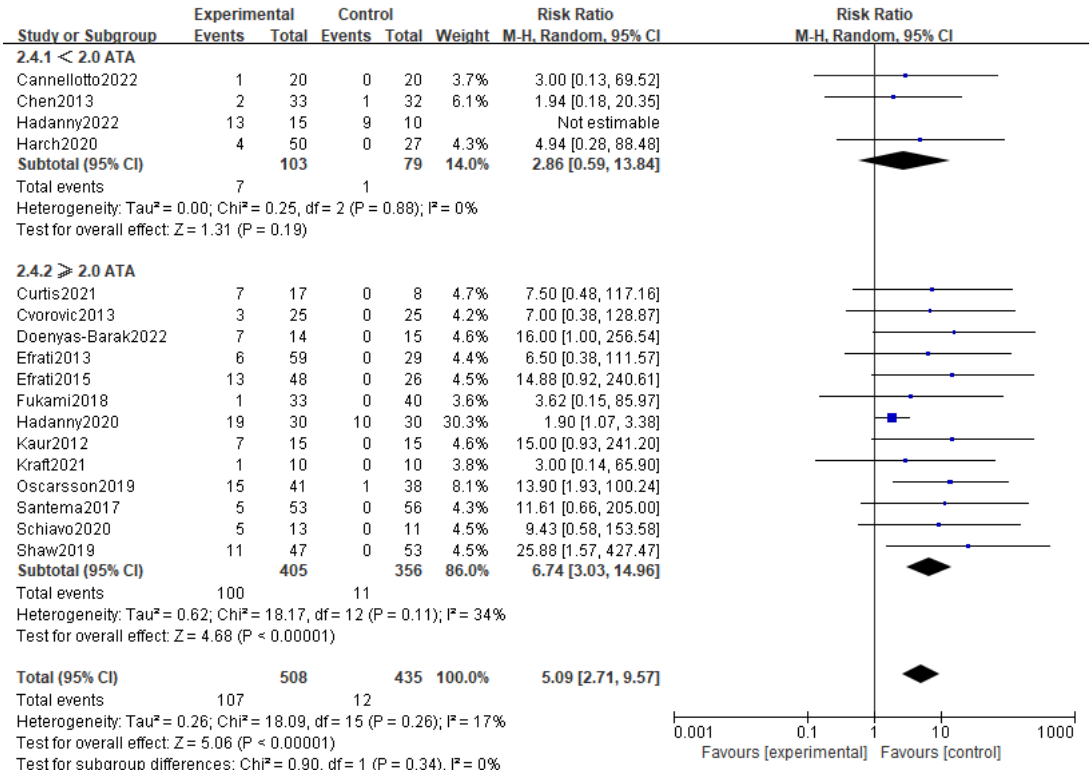

Figure 6

Analysis 2.4: 2.0ATA, ≥2.0ATA chamber pressures of HBOT versus any control group, any adverse event.CI: confidence intervaldf: degrees of freedom M-H: Mantel-Haenszel method of meta-analysis P: probability Z: Z score (standard score)

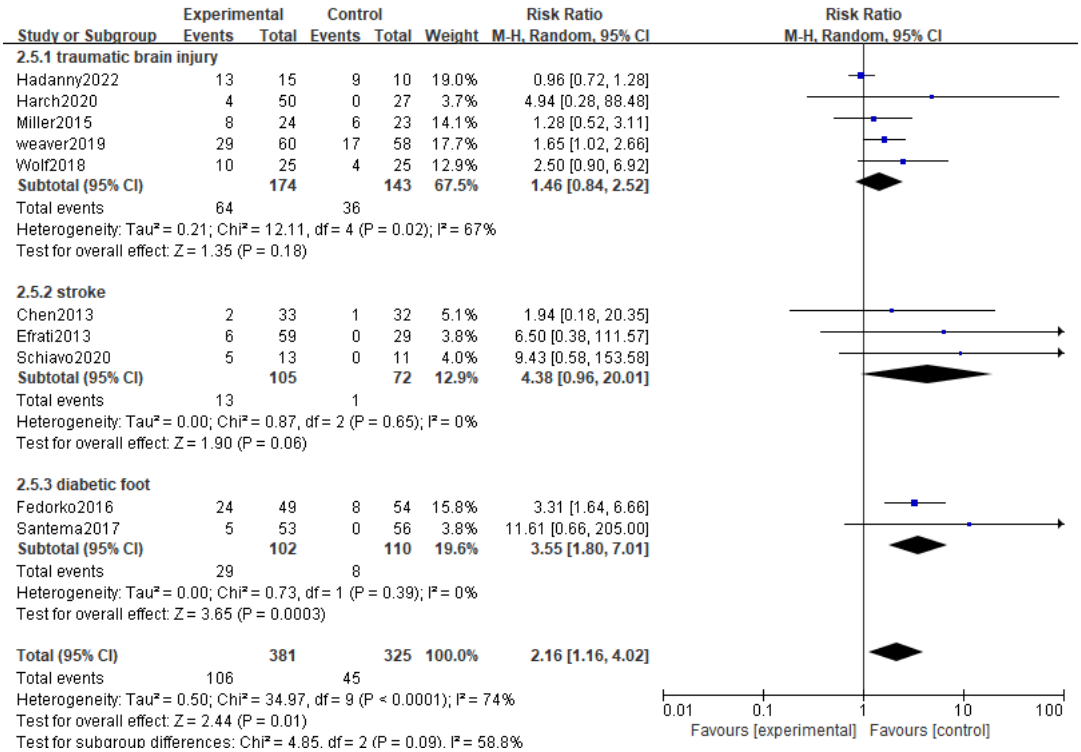

Figure 7

Analysis 2.5: HBOT in traumatic brain injury, stroke and diabetic foot versus any control group, any adverse event.CI: confidence intervaldf: degrees of freedom M-H: Mantel-Haenszel method of meta-analysis P: probability Z: Z score (standard score)