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Research article

Addition of hyperbaric oxygen therapy versus usual care alone for inflammatory bowel disease: A systematic review and meta-analysis

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ABSTRACT

Objective: Inflammatory bowel disease (IBD) is a chronic idiopathic inflammatory disease that includes ulcerative colitis (UC) and Crohn's disease (CD). Hyperbaric oxygen therapy (HBOT) involves breathing pure oxygen in a pressurized environment. Existing literature suggests that HBOT may be an effective therapy for IBD, but a quantitative analysis is lacking. This study aims to estimate the adjunctive role of HBOT in treating IBD and lowering its recurrence rate.

Design: Systematic review and meta-analysis.

Methods: The Cochrane Library, EMBASE, PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and Wanfang databases were systematically searched by two reviewers independently. Meta-analyses were performed using Review Manager (RevMan, version 5.3). A random-effects model was applied due to the heterogeneity between studies.

Results: Twenty-nine out of the initially identified 606 articles were covered in this review, with a total of 2151 patients (2071 for UC and 80 for CD). No randomized data of HBOT for CD were included. Among UC patients, usual care plus HBOT were more likely to achieve a clinical response than usual care alone (risk ratio [RR], 1.24; 95% confidence interval (CI), 1.17 to 1.31; $P < 0.001$). Subgroup analysis showed that the number of HBOT sessions had no statistically significant effect on overall efficacy ($P > 0.05$). The pooled data showed a lower recurrence rate in the usual care plus HBOT group (RR, 0.35; 95% CI, 0.24 to 0.53; $P < 0.001$). The standardized mean difference in the serum tumor necrosis factor level between HBOT and non-HBOT groups was -2.13 (95% CI, -3.09 to -1.18; $P < 0.001$). No severe adverse events of HBOT were observed.

Conclusions: HBOT might be an effective and safe adjunctive treatment for IBD. Further studies are required to investigate the optimal protocol of HBOT in IBD treatment.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic idiopathic inflammatory disease that includes ulcerative colitis (UC) and Crohn's disease (CD) (Sairenji et al., 2017). The global incidence and prevalence of IBD are rising. It is estimated that by 2030, the disease will affect 1% of people in the Western world (Tsai et al., 2021). IBD is typically discovered in patients between the ages of 20 and 29 (Nielsen et al., 2022). Patients with IBD usually suffer from physical dysfunctions such as abdominal pain, bloating, and diarrhea. Lesions are typically found in the large intestine or rectum (for UC) and throughout the gastrointestinal tract (for CD). Although the etiology of IBD remains largely unknown, it may involve a complex interplay of geographic location, inappropriate diet, genetics, and a weak immune response (Zhang et al., 2014). The natural history of IBD is diverse, ranging from mild symptoms to debilitating diseases that may result in hospitalization, surgery, and disability. Recurrence of IBD is common, and nearly one-third of patients suffer a relapse within 12 months of stopping biologics (Kennedy et al., 2016).

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The management of IBD has developed considerably in recent decades. In Europe, surgery rates have decreased over time, with 10–30% of CD patients and 5–10% of UC patients requiring surgery within 5 years (Zhao et al., 2021). IBD is not curable. The current goal of treatment is to minimize symptoms, improve quality of life, slow disease progression, and reduce complications as much as possible. The current standard treatment for IBD is medication, including anti-tumor necrosis factor biologics, agents that target leukocyte trafficking, interleukin (IL) 23 (Argollo et al., 2017), corticosteroids, aminosalicylates, antibiotics, supportive drugs, and immunosuppressive drugs (Ananthakrishnan et al., 2021). However, medication is usually accompanied by side effects that have to be evaluated thoroughly before treatment decisions (Seyedian et al., 2019). In recent decades, new nonpharmacological treatments have emerged, such as hyperbaric oxygen therapy (HBOT), mesenchymal stem cells, and anal fistula plugs.

HBOT is an alternative therapy during which patients inhale up to 100% oxygen at a pressure greater than one absolute atmosphere (ATA) in a pressurized chamber. The hyperbaric oxygen chamber was first constructed in 1834 by Junod to treat pulmonary disease under the pressure of 2–4 ATA (Jain et al., 2017). Hyperbaric oxygen could evoke high partial pressure of oxygen in all tissues, alleviate edema, activate fibroblasts and macrophages, and boost angiogenesis and collagen synthesis (Al-Waili et al., 2006). According to the Tenth European Consensus Conference on Hyperbaric Medicine, the accepted indications for HBOT include decompression illness, gas embolism, carbon monoxide poisoning, and brain injury (acute and chronic traumatic brain injury, chronic stroke, and post anoxic encephalopathy) (Mathieu et al., 2017). With the popularity of HBOT, some experts have called for an electronic registry system for the different indications of HBOT to provide optimal health services for patients (Shahram Oliaeia, 2020). In recent decades, numerous studies have explored the usefulness of HBOT for IBD. In 1989, Brady et al. reported the first case of using HBOT to treat severe perineal Crohn's disease (Brady et al., 1989). Then, Noyer et al. reported similar cases in 1999 (Noyer et al., 1999). Several reports have described the effectiveness of HBOT in the healing of UC (Buchman et al., 2001; Gurbuz et al., 2003; Dulai et al., 2017, 2018).

Although several reviews (Rossignol, 2012; Dulai et al., 2013, 2014; Singh et al., 2021) have suggested that HBOT was effective for treating IBD, they did not examine HBOT's potential applications in IBD adjuvant therapy or relapse prevention. The optimal dose of HBOT remains uncertain. In addition, quantitative analyses of inflammatory factors are lacking. Therefore, it is important to ensure the safety and efficacy of HBOT and to determine the optimal treatment regimen in the clinic. To address this issue, we performed a systematic review and meta-analysis, to capture the latest data to evaluate the response rate, recurrence rate, and serum tumor necrosis factor levels of IBD patients after receiving HBOT plus usual care. In addition, we tried to explore the optimal protocol of HBOT for IBD.

2. Methods

This article was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

2.1. Literature search

The search strategy is shown in Supplementary Text 1. Three authors (J.H.Y., W.B.H., and H.M.) developed a comprehensive search strategy. Subsequent searches were conducted for published literature in the electronic databases Medline via PubMed, Embase via Ovid, Cochrane Library, Web of Science, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Wanfang from Jan 1, 2000, to March 7, 2022. The search was performed using a combination of the following keywords and MeSH terms: IBD, inflammatory bowel diseases, colitis, Crohn, regional enteritis, ileocolitis, regional ileitis, granulomatous enteritis, jejunitis, ileitis, proctitis, proctocolitis, duodenitis, pancolitis, hyperbaric oxygenation, hyperbaric, HBOT. In addition, the authors manually retrieved documents from the reference lists of articles identified from the aforementioned databases.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) randomized controlled trials (RCTs), non-RCTs, and case series (n>=5), (2) studies in the English or Chinese language, (3) studies of IBD patients aged above 18 years, and (4) studies exploring the adjunctive use of HBOT under usual care. Usual care varies widely across countries and health systems, and we define usual care as de facto routine clinical care. In addition, we included studies published from 2000 to 2022 to capture the latest evidence. The exclusion criteria were as follows: (1) studies without information on the dose or duration of HBOT, (2) animal experiments, (3) studies that did not provide outcomes related to clinical response, recurrence, or tumor necrosis factor-alpha (TNF-α), and (4) duplicate publications, reviews, guidelines, commentaries, or meeting abstracts.

2.3. Outcome definitions

2.3.1. Overall response rate

The primary outcome was the overall response rate. Clinical response was defined as the basic disappearance or significant improvement of clinical signs and symptoms after treatment.

2.3.2. Recurrence rate

The secondary outcome was the recurrence rate. Recurrence referred to patients who had IBD symptoms again within 3–6 months.

2.3.3. TNF-α

The third outcome was the TNF-α level, which is a major proinflammatory cytokine involved in early inflammatory events.

2.3.4. Adverse events

The fourth outcome was the adverse event associated with HBOT.

2.4. Study selection and data extraction

Study selection was conducted independently by two reviewers (J.H.Y. and J.L.J.) in two successive rounds. Articles were first screened based on their titles and abstracts. Those identified as potentially eligible were then screened in full text. Consensus on inclusion was reached through discussion (by J.H.Y., J.L.J., and M.Z.).

Two authors (C.H. and J.L.J.) completed data extraction independently. Any divergence was finalized through discussion with the other two authors (J.H.Y. and W.B.H.). Finally, the data were summarized in a standardized worksheet of Excel for Windows 2010. The extracted data included basic information about the study (e.g., first author, publication year, country, trial design); the number of participants in the intervention and control groups; intervention details (HBOT protocol such as pressure, duration, course, and the number of treatment sessions); and outcomes (effective rate, clinical response, clinical remission, recurrence rate).

2.5. Risk of bias assessment

Two reviewers (J.L.J. and W.B.H.) separately evaluated the bias risk. Disagreements were discussed with a third reviewer (C.H.) until a consensus was reached. Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) in the Cochrane Handbook (Higgins JPT, 2022) was used to assess the risk of bias of RCTs, including (1) random sequence generation, (2) allocation concealment, (3) blinding of participants personnel and outcome assessment, (4) incomplete outcome data, and (5) selective reporting. We assigned one of three levels to each domain: low risk of bias, unclear (uncertain risk of bias), or high risk of bias.

Table 1. Characteristics of included studies on hyperbaric oxygen therapy for ulcerative colitis.

Author, year, country	Patients (N)		Intervention		Comparison	Outcome	Study design
	Intervention	Control	HBOT protocol	HBOT sessions			
Dulai (2018), USA	10	8	at 2.4 ATM for 90 min/session, one session per day for 10 days	10	1 to 1.34 ATA while breathing room air (21% oxygen)	Mayo score, clinical response, clinical remission, endoscopic remission	RCT
Pagoldh (2013), Sweden	10	8	at 2.4 ATM for 90 min/session, 5 days/week, for 6 consecutive weeks*	30	the standard routine of intensive UC treatment with initial intravenous glucocorticosteroid treatment	SF-36, IBDQ, fecal weight, Mayo score	RCT
Yang (2016), China	69	69	at 0.20 MPa for 80 min/session, 10 days/course, one-week interval/course, for 3 consecutive courses*	30	sulfasalazine therapy	effective rate, recurrence rate, clinical response, clinical remission	RCT
Zhang (2004), China	13	13	at 0.22 MPa for 90 min/session, one session per day for 10 days*	10	sulfasalazine therapy and enema therapy	Baron score, effective rate, clinical response, clinical remission	RCT
Zhang (2013), China	40	40	at 2 ATA for 120 min/session, one session/day, 10 sessions per course for 3 courses*	30	enema therapy with traditional herbal medicine	effective rate, clinical response, clinical remission, recurrence rate	RCT
Zhong (2019), China	25	25	at 0.25 MPa for 100 min/session, one session per day for 4 consecutive weeks*	28	mesalazine therapy	Modified Mayo score, serum, SOD, recurrence rate	RCT
Huang (2016), China	40	38	at 0.25 MPa for 100 min/session, one session per day for 4 consecutive weeks*	28	mesalazine therapy	TNF-α, IL-10, SOD, recurrence rate, effective rate, clinical response, clinical remission	RCT
Li (2009), China	42	38	at 2 ATA for 120 min/session, one session per day for 4 consecutive weeks*	28	sulfasalazine therapy and enema therapy	clinical response, clinical remission	RCT
Luo (2014), China (Luo et al., 2014)	40	38	at 240 kPa for 90 min/session, one session/day for 4 weeks*	28	sulfasalazine therapy	clinical response, clinical remission	RCT
Nie (2011), China	73	65	at 200 kPa for 90 min/session, one session/day for 4 weeks*	28	sulfasalazine therapy	TNF-α, IL-6, effective rate, clinical response, clinical remission	RCT
Shen (2000), China	8	17	at 0.24 MPa for 90 min/session, 10 sessions per course for 2–3 courses with 2-day-interval*	20–30	sulfasalazine therapy and enema therapy	effective rate, clinical response, clinical remission	RCT
Wang (2011), China	30	30	at 0.2 MPa for 100 min/session, one session/day, 10 days/course for 4 courses with 3-day-interval*	40	sulfasalazine therapy	effective rate, clinical response, clinical remission, recurrence rate	RCT
Wang (2020), China	70	70	at 0.24 MPa for 130 min/session, one session per day, 10 days/course for 6 courses with 2-day-interval*	60	mesalazine therapy	effective rate, clinical response, recurrence rate	RCT
Yin (2008), China	48	46	at 240 kPa for 90 min/session, one session per day, 7 days/course for 4 courses*	28	sulfasalazine therapy	TNF-α, IL-6, effective rate, clinical response	RCT
Zhan (2013), China	15	15	at 0.2 MPa for 120 min/session, one session per day, 10 days/course for 3 courses*	30	sulfasalazine therapy	effective rate, clinical response, clinical remission	RCT
Zhu (2009), China	19	19	at 2.0 ATA for 90 min/session, one session per day, 10 days/course with 3-day-interval, for 3 months*	70	sulfasalazine therapy	effective rate, clinical response, clinical remission, recurrence rate	RCT
Deng (2018), China	60	60	at 0.2 MPa for 115 min/session, one session per day, 10 days/course for 3 courses*	30	mesalazine therapy	clinical response, clinical remission, TNF-α, IL, SOD, MAD, IgA, IgG, IgM, ADMA	RCT
Qiao (2014), China	36	34	at 0.2 MPa for 100 min/session, one session per day, 15 days/course for 3 courses with an interval of 7 days*	45	sulfasalazine therapy	clinical response, clinical remission, recurrence rate	NCT
Yuan (2016), China	90	78	at 0.2 MPa for 100 min/session, one session per day, 14 days/course for 3 courses with an interval of 7 days*	42	sulfasalazine therapy	clinical response, clinical remission, TNF-α, IL	NCT
Xu (2001), China	21	15	at 0.2 MPa for 110 min/session, one session per day, 12 days/course for 3 courses with an interval of 7 days*	36	sulfasalazine therapy	effective rate	NCT

(*continued on next page*)

Table 1 (*continued*)

Author, year, country	Patients (N)		Intervention		Comparison	Outcome	Study design
	Intervention	Control	HBOT protocol	HBOT sessions			
Fu (2001), China	23	21	at 0.12 MPa for 100 min/session, one session per day, 10 days/course for 4 courses*	40	sulfasalazine therapy	DAI	NCT
Yang (2012), China	141	135	at 0.2 MPa for 105 min/session, one session per day for 8 weeks*	56	sulfasalazine therapy	clinical response, clinical remission	NCT
Zhang. P., 2004, China	42	40	at 2 ATA for 120 min/session, one session/day, 10 sessions/course for 2 courses*	20	sulfasalazine therapy	SOD, MAD, SOD, effective rate, recurrence rate, clinical response, clinical remission, Ig	NCT
Zhang (2001), China	42	40	at 2 ATA for 120 min/session, one session/day, 10 sessions/course for 2 courses*	20	sulfasalazine therapy	effective rate, recurrence rate, Ig	NCT
Wang (2003), China	36	34	at 0.2 MPa for 120 min/session, one session per day, 10 days/course for 3 courses*	30	sulfasalazine therapy	effective rate, clinical response, clinical remission	NCT
Bekheit (2016), Egypt	32	-	at 2.8 ATA for 65 min, five sessions per week for eight consecutive weeks*	40	-	effective rate, clinical response, clinical remission,	case series

Abbreviations: HBOT, hyperbaric oxygen therapy; ATA, atmospheric pressure; min, minutes; kPa, kilopascal; MPa, Megapascal; TNF-α, tumor necrosis factor alpha; IL, interleukin; DAI, disease activity index; SOD, superoxide dismutase; MAD, malondialdehyde; Ig, immunoglobulin; ADMA, asymmetric dimethylarginine; NCT, non-randomized controlled trial; RCT, randomized controlled trial.

* The usual care of the control group was also performed in the HBOT group.

The quality of non-RCTs was evaluated according to the Methodological Index for Nonrandomized Studies (MINORS) (Slim et al., 2003). The MINORS scoring system includes eight items (a maximum score of 16) for noncomparative studies and twelve items (a maximum score of 24) for comparative studies. Scores for each item ranged from 0 to 2 (0, not reported; 1, reported but poorly or inadequately done; 2, reported but well and adequately done). Studies scoring >12/16 or >19/24 were considered high quality.

2.6. Statistical analysis

Meta-analysis was performed using Cochrane RevMan software (version 5.3). A statistically significant effect was assumed if $P < 0.05$. Pooled results were expressed as the standardized mean difference (SMD) for continuous data and the risk ratio (RR) for categorical data. Forest plot tests were conducted, and heterogeneity was examined by meta-regression analysis. A subgroup analysis was performed for the number of HBOT sessions.

2.7. Assessment of heterogeneity

For each outcome, heterogeneity across studies was quantified using the I^2 statistic, which summarized the percentage of variability due to study heterogeneity. The random-effects model was used considering clinical heterogeneity from differences in concomitant treatments, treatment eras, definitions of success, and HBOT regimen.

3. Results

3.1. Study characteristics

The initial search strategy yielded 606 publications. Of those, 475 were excluded after reviewing the titles and abstracts. Subsequently, 131 papers were retrieved in the full text, and 29 studies were included in our final analysis. Among the 29 studies, we had 16 RCTs, 11 non-RCTs, and two case series (as shown in Table 1 and Table 2). The flow diagram is

Table 2. Characteristics of included studies on hyperbaric oxygen therapy for Crohn's disease.

Author, year, country	Patients(N)		intervention		Comparison	Outcome	Study design
	Intervention	Control	HBOT protocol	HBOT Sessions			
Lansdorp (2021), The Netherlands	20	8	at 243–253 kPa for 80 min/session, one session per weekday for 8 weeks*	40	usual care	PDAI, MRI, clinical response and remission, VAS, IBDQ, a validated decision regret scale	NCT
Feitosa (2016), Brazil	29		at 2.4 ATA for 120 min/session, one session per day	29	-	closure of enterocutaneous fistulas, complete healing of pyoderma gangrenosum and perineal Crohn's disease, overall success rate	NCT
Iezzi (2011), Brazil	14		at 2.4 ATM for 120 min, one session per day	ranged from 10 to 50	-	clinical symptoms, effective rate	NCT
Agrawal (2015), Australia	9		at 2.0–2.4 ATM for 90 min, one session per day	22	-	clinical symptoms, MRI improvement, effective rate	case series

Abbreviations: kPa, kilopascal; PDAI, perianal disease activity index; MRI, magnetic resonance imaging; VAS, visual analog scale; IBDQ, Inflammatory Bowel Disease Questionnaire; ATM, atmosphere of pressure; ATA, atmospheric pressure; NCT, nonrandomized controlled trial.

* The usual care of the control group was also performed in the HBOT group.

shown in Figure 1. These studies reported a total of 2151 patients (2071 for UC and 80 for CD).

3.2. Risk of bias and heterogeneity

A summary of the risk of bias for the RCTs is provided in Figures 2 and 3. Six of the included studies (Pagoldh et al., 2013; Li, 2009; Zhu, 2009; Shen, 2000; Zhong et al., 2019; Yin, 2008) were judged to be at low risk of random sequence generation, and the remaining studies were at high risk (Li, 2009; Nie, 2011; Luo, 2014; Zhan, 2013; Zhang, 2004a, 2013; Yang, 2016; Shen, 2000; Zhong, 2019), mainly due to the lack of specific randomization methods. All sixteen studies were at a high or unclear risk of allocation concealment (Pagoldh et al., 2013; Dulai et al., 2018; Zhan, 2013; Li, 2009; Zhang, 2004a, 2013; Yang, 2016; Nie, 2011; Luo, 2014; Huang, 2016; Wang, 2011, 2020; Zhu, 2009; Shen, 2000; Yin, 2008; Zhong, 2019), as they did not show whether the allocation was concealed. Only one study was assessed as having a low risk of performance bias (Dulai et al., 2018), and the remaining studies were judged to have a high or unclear risk of performance bias and detection bias (Pagoldh et al., 2013; Zhan, 2013; Li, 2009; Zhang, 2004a, 2013; Yang, 2016; Nie, 2011; Luo, 2014; Huang, 2016; Wang, 2011, 2020; Zhu, 2009; Shen, 2000; Yin, 2008; Zhong, 2019) because they did not adopt blinding. Fourteen studies were at low risk of attrition bias because of the relatively complete outcome data. Regarding reporting bias, only one study (Pagoldh et al., 2013) was at low risk, and other studies were at unclear risk (Dulai et al., 2018; Zhan, 2013; Li, 2009; Zhang, 2004a, 2013; Yang, 2016; Nie, 2011; Luo, 2014; Huang, 2016; Wang, 2011, 2020; Zhu, 2009; Shen, 2000; Yin, 2008; Zhong, 2019), mainly due to the lack of follow-up rates.

The quality of the non-RCTs is shown in Table 3. The average MINORS score for comparative and noncomparative studies was 15 and 7, respectively. Consecutive patients, appropriate endpoints, an adequate control group, concurrent trials, and consistent baselines were the most frequent criteria for high MINORS scores. Lack of prospective collection of data and study size calculation and biased assessment of the study endpoint were the most common reasons for low MINORS scores.

3.3. Effects of interventions

Heterogeneity for these three outcomes is as follows: overall response rate ($I^2 = 16\%$, $P = 0.26$), recurrence rate ($I^2 = 0\%$, $P = 0.54$), and TNF-α level ($I^2 = 92\%$, $P < 0.01$).

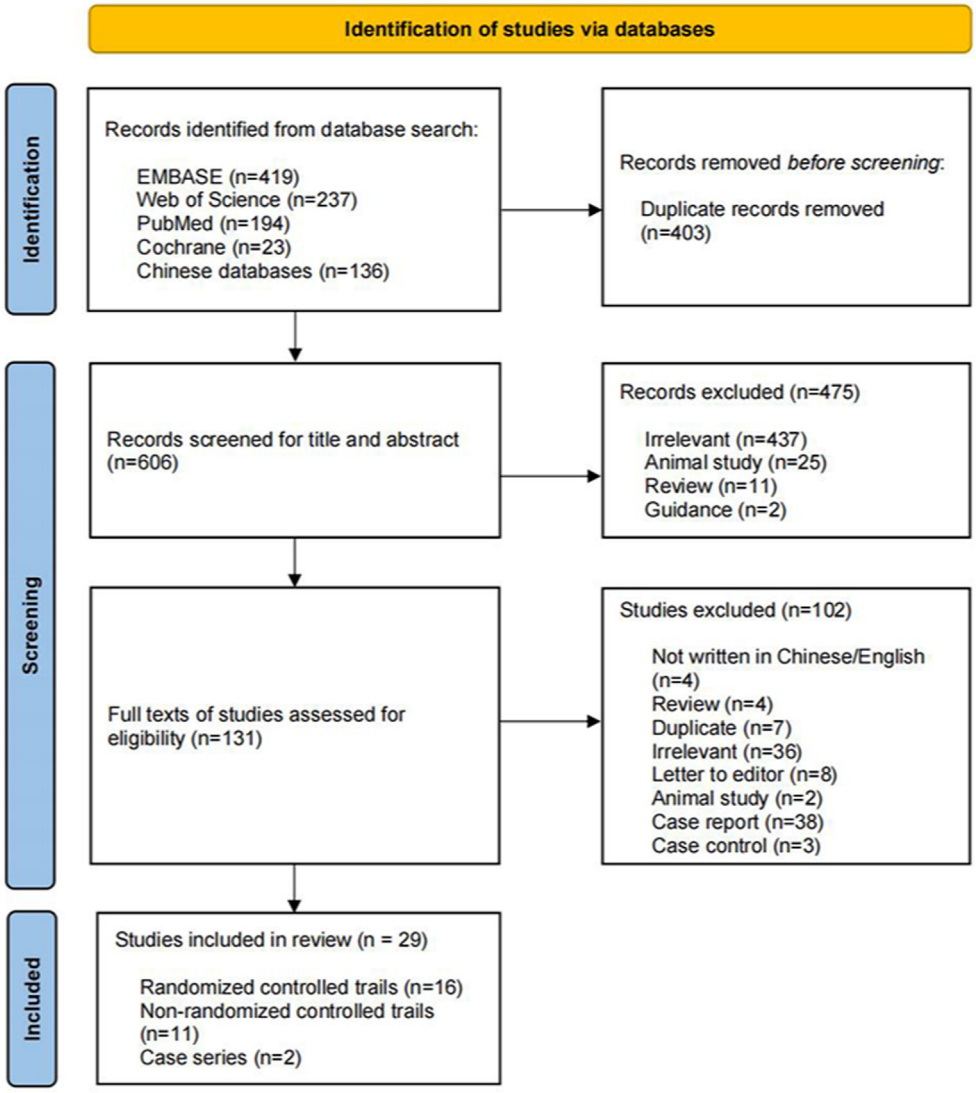

Figure 1. PRISMA flowchart depicting the process of study selection for the systematic review.

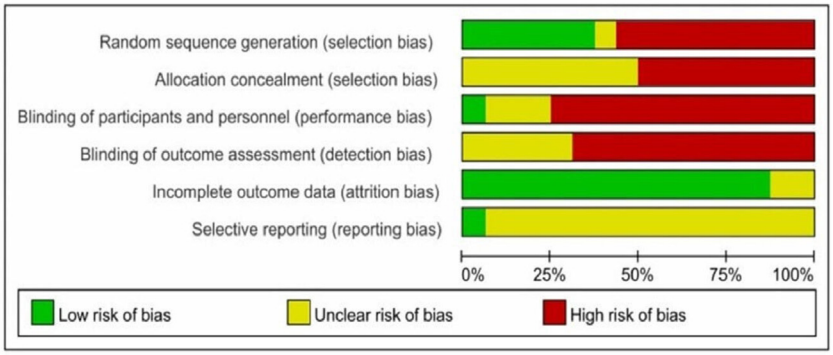

Figure 2. Risk of bias graph: authors' judgments about each risk of bias item presented as percentages across all included randomized controlled trails.

3.3.1. Ulcerative colitis

3.3.1.1. Overall response rate. 1075 patients with UC received HBOT. HBOT plus usual care was more effective than usual care alone in the treatment of UC (RR, 1.24; 95% confidence interval [CI], 1.17 to 1.31; $P < 0.001$). Subgroup analysis by number of HBOT sessions did significantly affect the outcome of UC: HBOT sessions less than 20 (RR, 1.26; 95% CI, 1.09 to 1.45; $P < 0.001$, $I^2 = 39\%$), HBOT sessions between 20 and 40 (RR, 1.21; 95% CI, 1.13 to 1.29; $P < 0.001$, $I^2 = 0\%$), and HBOT sessions more than 40 (RR, 1.35; 95% CI, 1.14 to 1.59; $P < 0.001$, $I^2 = 41\%$) (Figure 4). However, no significant differences were observed among the three subgroups ($P = 0.48$).

3.3.1.2. Recurrence rate. Patients with UC who received usual care plus HBOT had a lower recurrence rate than those who received usual care only, with an RR of 0.35 (95% CI, 0.24 to 0.53, $P < 0.001$, $I^2 = 0\%$) (Figure 5).

3.3.1.3. TNF-α. The findings suggested that HBOT could lower TNF-α levels in UC patients. The SMD was -2.13 (95% CI, -3.09 to -1.18, $P < 0.001$, $I^2 = 92\%$) (Figure 6).

3.3.2. Crohn's disease

For CD, this study included three non-RCTs and one case series, which are shown in Table 2. HBOT sessions were administered to 72 patients with CD. The included studies showed that HBOT effectively treated CD, and even combined with usual care to achieve complete healing of refractory CD. In addition, continuing Mycobacterium avium ss paratuberculosis treatment after the conclusion of HBOT may be successful in preventing CD recurrence. A meta-analysis was not carried out since there were no randomized data on CD patients receiving HBOT.

3.4. Adverse events

Nine of the 1147 patients (0.78%) had mild adverse events. Five patients with CD had mild to moderate middle ear baroreflex signs during otoscopy, and three required tympanostomy tubes to complete the HBOT (Lansdorp et al., 2021). In addition, a patient with UC suffered skin rashes (Zhang, 2004b). No other severe side effects were reported.

4. Discussion

In this systematic review of 27 clinical studies and two observational studies, we found that HBOT could be combined with usual care to improve IBD outcomes without severe side effects and reduce the recurrence rates of UC. Although previous systematic reviews (Singh et al., 2021; Rossignol, 2012; Dulai et al., 2013, 2014) reported the efficacy of HBOT in treating IBD, they did not explore the adjunctive effects of HBOT in IBD patients who underwent usual care. Our study

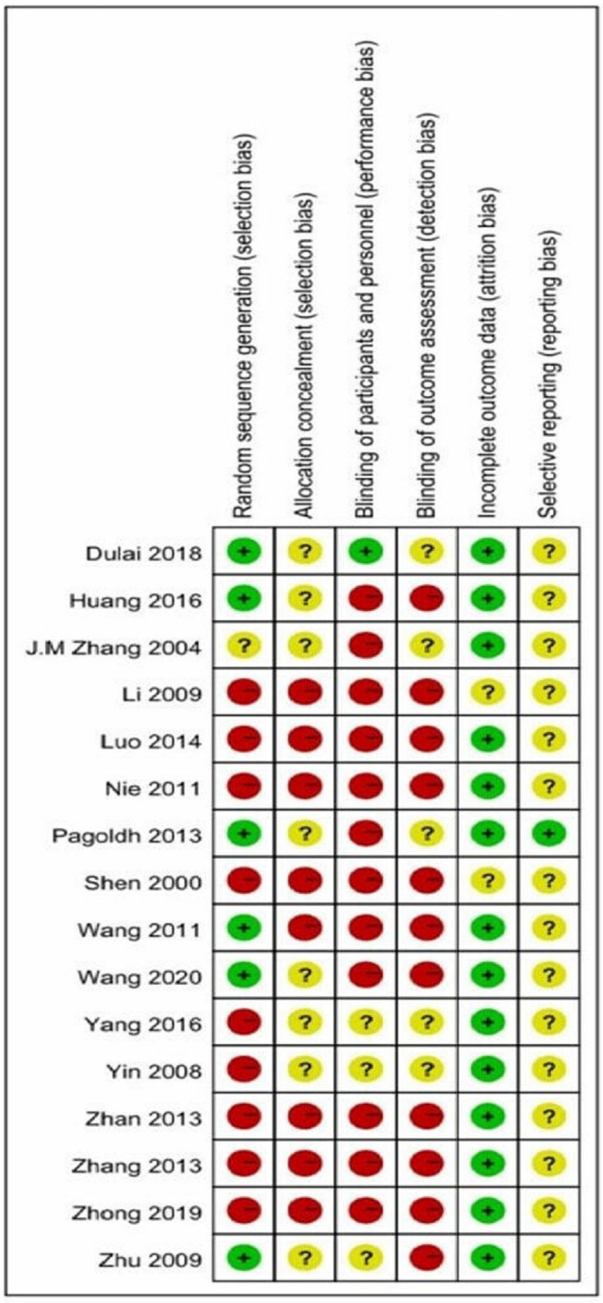

Figure 3. Risk of bias summary: authors' judgments about each risk of bias item for each included randomized controlled trail.

Table 3. Quality assessment of the included nonrandomized controlled trials using the Methodological Index for Nonrandomized Studies (MINORS).

Evaluation	Qiao et al., 2014	Yuan et al., 2016	Fu et al., 2001	Feitosa et al., 2016	Zhang et al., 2001	Xu et al., 2001	Yang 2012	Zhang.P 2004	Lansdorp 2021	Lezzi 2011
1. A clearly stated aim	2	2	1	2	2	0	1	0	2	2
2. Inclusion of consecutive patients	2	2	2	1	1	2	2	2	2	0
3. Prospective collection of data	0	0	0	0	0	0	0	0	2	1
4. Endpoints appropriate to the aim of the study	2	2	2	1	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	0	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	0	0	0	2	0	1	2	2	1
7. Loss to follow up less than 5%	0	2	2	2	1	2	2	2	2	2
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0
9. An adequate control group	2	2	2	-	2	2	2	2	2	-
10. Contemporary groups	2	2	2	-	2	2	2	2	2	-
11. Baseline equivalence of groups	2	2	1	-	2	1	2	2	1	-
12. Adequate statistical analyses	0	0	0	-	2	2	2	2	2	-
Total score	14	14	12	6	16	13	16	16	19	8

systematically reviewed the efficacy between the usual care plus HBOT arm and the usual care arm and performed a subgroup analysis of different HBOT sessions. In addition, this study performed a quantitative analysis of recurrence rates and the level of inflammatory factors, which was lacking in previous systematic reviews.

4.1. Overall response rate

This systematic review showed that usual care supplemented with HBOT was more effective in treating IBD than usual care alone. This was consistent with previous studies (Dulai et al., 2013, 2014; Rossignol, 2012; Singh et al., 2021). In addition, HBOT was effective in treating refractory complications such as metastatic CD and perianal fistulas (Lansdorp et al., 2021)(Lansdorp et al., 2020). The underlying mechanism of HBOT in IBD is not yet fully understood. Previous studies have suggested that elevated pressure, hyperoxia, and modulation of oxidative stress from HBOT may contribute to its therapeutic effects (Rossignol, 2012). HBOT produces reactive oxygen and reactive nitrogen species, which act as signaling molecules in the pathway of injury healing (Novak et al., 2016). A recognized mechanism of UC is mucosal hypoxia, and

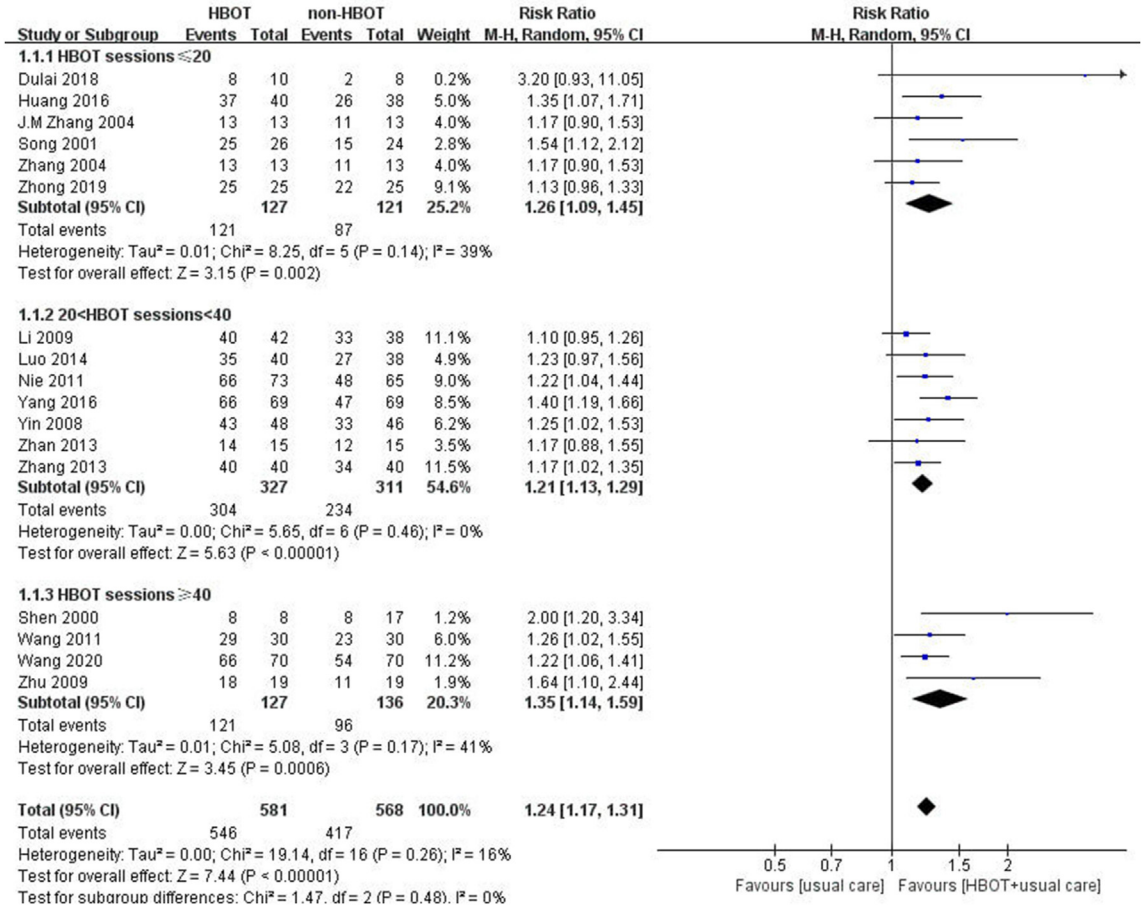

Figure 4. Forest plot quantifying the RR of the response rate for ulcerative colitis.

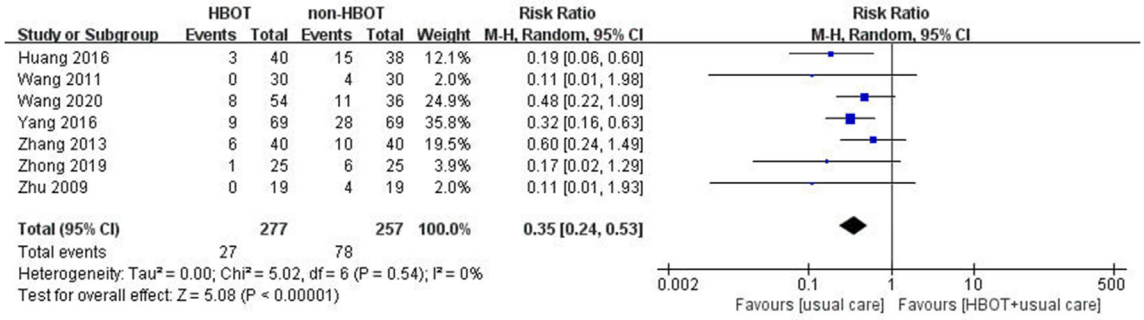

Figure 5. Forest plot quantifying the RR of recurrence rate for ulcerative colitis.

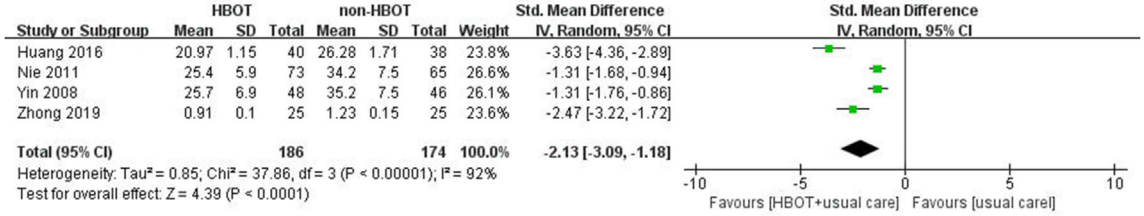

Figure 6. Forest plot quantifying the SMD of TNF-α for ulcerative colitis.

HBOT may promote mucosal healing by raising stem cells in the injured areas (Bekheit et al., 2016). Moreover, ventilating 100% oxygen at high pressure would increase oxygen partial pressure in the tissues. HBOT provides an ideal environment for the immune system by ameliorating tissue hypoxia and inducing a bacteriostatic response to microorganisms (Memar et al., 2019).

Paradoxically, Pagoldh et al. (2013) found no significant differences between the HBOT group and the conventional treatment group of IBD patients in Mayo score, laboratory tests, and fecal weight. The reason may be the limited number of subjects (10 for the HBOT group and eight for the control group), the open-label design, or the inaccurate HBOT protocol. Studies with larger sample sizes are needed to validate the effectiveness of HBOT in patients with IBD.

The subgroup analysis found no statistically significant difference in efficacy whether the number of HBOT sessions was less than 20, between 20 and 40, or more than 40. In the included studies, the minimum number of HBOT sessions was 10, and the maximum was 70. Few reviews have analyzed the dose-response effect of HBOT on IBD. Dulai (Dulai et al., 2020) found that 5-day HBOT was superior to 3-day treatment in improving disease activity and normalizing rectal bleeding. More clinical studies are needed to investigate the optimal doses of HBOT for IBD.

4.2. Recurrence rate

The results showed that usual care combined with HBOT could lower the recurrence rate of UC. Previous studies found that subclinical inflammation usually persisted even in the remission stage, especially in patients with CD, leading to an increased risk of stenosing or penetrable complications (Wright et al., 2018). HBOT reduces the recurrence rate by increasing oxygen content, thereby downregulating the expression of hypoxia-inducible factor-1α (HIF-1α). An immunohistochemical study (Song et al., 2018) showed that the expression of the inflammatory factors (TNF-α, IL-6, vascular endothelial growth factor, and HIF-1α) detected in the HBOT group was lower than that in the non-HBOT group, suggesting that HBOT suppresses the inflammatory response during wound recovery in patients with IBD. Therefore, HBOT may not only attenuate the inflammatory response during treatment and relieve tissue hypoxia, but also improve patients' immunity and prevent a subsequent recurrence.

4.3. TNF-α

TNF-α is a key cytokine in the inflammatory response and plays an important role in the pathogenesis of IBD. This meta-analysis showed that HBOT combined with usual care significantly reduced serum TNF-α levels in patients with IBD. Since anti-TNF drugs for the treatment of IBD were first introduced decades ago, they have become widely accepted by many patients (Ben-Horin et al., 2014). A narrative review in 2018 showed that HBOT could alleviate the symptoms of IBD by reducing proinflammatory cytokine concentrations, inflammatory biomarkers, and oxidative stress (Mohamed, 2018). HBOT temporarily inhibited the stimulus-induced production of proinflammatory cytokines, including TNF-α. HIF-1α is a crucial mediator in the hypoxic response, and its expression is concentrated in both UC and CD (Bhat et al., 2022). Activated HIF-1α can bind to the promoter of the TNF-α gene, leading to increased expression of TNF-α. HBO can reduce the expression of HIF-1α (Ostrowski et al., 2005), thereby diminishing inflammation and enhancing mucosal closure. In patients with CD, HBOT decreases IL-1, IL-6, and TNF-α levels (Weisz et al., 1997).

4.4. Adverse events

This study found that nine of 1147 patients with IBD experienced mild adverse events while receiving HBOT. No severe side effects were observed. Therefore, HBOT may be considered a safe adjunctive therapy for the treatment of IBD. The side effects of HBOT are from both the physiological response to the highly pressurized hyperoxic environment and the psychological response to the closed treatment room. Middle ear barotrauma (MEB) is a common complication of HBOT. Patients might experience balance difficulties in the ear, a sense of pressure, earache, and uncomfortable feelings while compressing (Jain et al., 2017). Sinus and paranasal barotrauma is the second most common barotrauma after MEB. HBOT may also lead to oxygen toxicity (Hadanny et al., 2019), ocular complications, hyperoxia myopia (McMonnies et al., 2015), claustrophobia (Liu et al., 2012), and hypoglycemia (Jain et al., 2017).

However, these described side effects are rare and self-limiting and can often be prevented with proper screening (Hoggan et al., 2014). Studies have shown that most of the complications of HBOT occur when the applied pressure exceeds 2.0 ATA (Oliaei et al., 2021). Therefore, it may be safe to keep the pressure of HBOT below 2.0 ATA.

Some limitations do exist in this study. First, meta-analyses were only carried out for UC patients because there were no randomized clinical trials for CD patients. Second, this study only examined the efficacy of various HBOT sessions and did not analyze different HBOT pressures due to high heterogeneity.

5. Conclusion

In conclusion, this systematic review suggests that HBOT might be an effective and safe adjunctive therapy for the treatment of IBD. For UC, HBOT might help to reduce relapses and lower serum TNF-α levels. More high-quality studies are warranted to explore the optimal regimen of HBOT in IBD, especially in CD.

5.1. Registration and protocol

The PROSPERO trial registration number is CRD42021250619.

Declarations

Author contribution statement

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

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