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Can preventive hyperbaric oxygen therapy optimise surgical outcome?

A systematic review of randomised controlled trials

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BACKGROUND A primary underlying cause of postoperative complications is related to the surgical stress response, which may be mitigated by hyperbaric oxygen therapy (HBOT), the intermittent administration of oxygen at a pressure higher than the atmospheric pressure at sea level. Promising clinical studies have emerged suggesting HBOT's efficacy for reducing some postoperative complications. Notwithstanding, the effectiveness (if any) of HBOT across a range of procedures and postoperative outcomes has yet to be clearly quantified.

OBJECTIVE This systematic review aimed to summarise the existing literature on peri-operative HBOT to investigate its potential to optimise surgical patient outcome.

DESIGN A systematic review of randomised controlled trials (RCTs) with narrative summary of results.

DATA SOURCES MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials were searched without language restrictions through to 19 June 2018.

ELIGIBILITY CRITERIA Studies were included if they involved patients of any age undergoing any surgical procedure and provided with at least one HBOT session in the peri-operative period. Two independent reviewers screened the initial identified trials and determined those to be included. Risk of bias was assessed using the Cochrane Risk of Bias tool for RCTs.

RESULTS The search retrieved 775 references, of which 13 RCTs were included (627 patients). Ten RCTs (546 patients) reported treatment was effective for improving at least one of the patient outcomes assessed, while two studies (55 patients) did not find any benefit and one study (26 patients) found a negative effect. A wide range of patient outcomes were reported, and several other methodological limitations were observed among the included studies, such as limited use of sham comparator and lack of blinding.

CONCLUSION Peri-operative *preventive* HBOT may be a promising intervention to improve surgical patient outcome. However, future work should consider addressing the methodological weaknesses identified in this review.

TRIAL REGISTRATION The protocol (CRD42018102737) was registered with the International ProspectiveRegister of Systematic Reviews (PROSPERO).

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Introduction

The number of surgical procedures performed globally continues to rise.[1] Despite advancements in peri-operative care, up to 50% of patients who undergo elective major surgery will experience postoperative complications.[2,3] Two of the most common complications are surgical site infections[4] and anastomotic leaks.[5] Postoperative complications contribute to an increased risk of re-operation,[2] prolonged length of stay,[2] decline in quality of life,[2] morbidity and mortality.[2,6] Furthermore, there is a five-fold cost increase to the healthcare system when patients experience a severe complication.[3] For all these reasons, the peri-operative optimisation of surgical patients to prevent postoperative complications is critical.

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Postoperative complications involve complex multifactorial and interrelated processes and several pathophysiological pathways, which have been reviewed extensively elsewhere.[7–13] In brief, a key underlying factor for postoperative complications, among many different elements, is the classical 'surgical stress response', which places increased demands on patients' hormonal, metabolic and immunological systems.[14–16] The surgical stress response is described as a noninfectious systemic inflammation associated with neuroendocrine and metabolic dysregulation.[7,8] At the cellular and molecular levels, the stress response is classically characterised by an activation of the hypothalamic-pituitary-adrenal (HPA) axis resulting in increased cortisol, a sympathetic activation and production of systemic pro-inflammatory cytokines. Through mineralocorticoid and glucocorticoid receptors in the cytosol, cortisol induces a series of effects. Genomic effects modify gene and protein expression, for example coding for inflammation, metabolism, angiogenesis and electrolytes homeostasis. Nongenomic effects lead to endothelial dysfunction, tissue remodelling, immunomodulation and oxidative stress.[7]

The immunological response is central to dysregulations originating from the surgical stress response. Due to cell damage, several cells such as macrophages and neutrophils produce a proinflammatory response with increased interleukins IL-1, 6, 8 and tumour necrosis factor alpha (TNF-α),[10] while impeding the anti-inflammatory response with a decrease in IL-10.[17] Clinically, IL-6 is associated with the 'magnitude of operative injury' and the severity of the systemic inflammatory response.[10,18]

The production of radical oxygen species represents one of the many signalling pathways involved in postoperative complications. In addition to the surgical procedure itself, ischemia/reperfusion phenomenon (e.g. use of a limb Tourniquet, variation of intraabdominal pressure during laparoscopy) almost consistently results in increased oxidative stress.[9] ROS alter basic cell components (e.g. proteins, lipids and DNA), which are associated with cellular damage, as well as endothelium and organ dysfunction postoperatively.[9,10]

The overall stress response cascade also dysregulates catecholamines and insulin resistance, resulting in hyperglycaemia, and leads to hypermetabolism and hypercatabolism.[9–11] The surgical stress response associated with the ischemia/reperfusion phenomenon can further impede tissue perfusion, particularly for debilitated tissues in the presence of comorbidities such as diabetes or radiation therapy. These molecular, cellular and pathophysiological cascades can ultimately impair 'immune function and wound healing', and lead to multiorgan dysfunction and failure such as cardiovascular failure, ileus, hyperglycaemia, impaired homeostasis and mortality, especially in the context of major surgical procedures on frail patients.[8,10,11,16]

Preventing or reducing the inflammatory stress response induced by surgery has been proven effective to improve patient outcome, for example with the enhanced recovery after surgery (ERAS) protocol.[8,11] Further mitigating the surgical stress response, such as by either pharmacological or nonpharmacological ways, may help to decrease the occurrence and severity of postoperative complications, and subsequently lower human and financial healthcare costs.

Hyperbaric oxygen therapy (HBOT) for clinical use is defined as breathing 100% oxygen at a pressure more than 1.4 atmosphere absolute (ATA).[19] Among others, established indications for HBOT include radiation cystitis or enteritis, osteoradionecrosis, chronic osteomyelitis and chronic wound healing, in particular in the context of microangiopathy due to diabetes or radiation therapy. HBOT has also been used for preconditioning, as it upregulates defence mechanisms against subsequent ischemia.[11]

At the biological level, HBOT improves neovascularisation and postischemic tissue survival, promotes osteogenic process, has a bacteriostatic and bactericidal effect, and modulates inflammatory mediators (anti-inflammatory effect).[20] Breathing 100% oxygen under high pressure improves healing and tissue survival after ischemia via complex molecular and cellular cascades involving beta 2 integrin,[20] decreased pro-inflammatory cytokines, increased anti-inflammatory cytokines, induction of hypoxia-inducible factor (HIF), vascular endothelial growth factor and others.[21–23]

Although HBOT enhances ROS production, preclinical data show that the overall oxidative response paradoxically improves outcome following reperfusion injuries of various organs, for example brain, liver, muscles or heart.[24] Prophylactic HBOT also improves tolerance to ischemia in animals.[24] While the precise mechanisms are not yet fully understood, laboratory evidence suggests that HBOT temporarily inhibits neutrophils adhesion to endothelial cells via beta 2 integrin, which in turn decreases the ROS produced by neutrophils sequestered in the endothelium.[24,25] HBOT also leads to production of anti-inflammatory proteins and antioxidants enzymes.[24,25]

Promising clinical studies have emerged suggesting HBOT's efficacy for reducing some postoperative complications, including following coronary artery bypass grafting.[26,27] Notwithstanding, the effectiveness (if any) of HBOT across a range of procedures and postoperative outcomes has yet to be clearly quantified.

Objectives

We aimed to systematically summarise the existing literature on the peri-operative use of HBOT to optimise surgical patient outcomes.

Materials and methods

Protocol

This review was planned and conducted according to A Measurement Tool to Assess Systematic Reviews (AMSTAR-2) standards.[28] and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[29] The protocol (CRD42018102737) was registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Eligibility criteria

Studies were included if they involved patients of any age undergoing any surgical procedure and provided with at least one HBOT session in the peri-operative period. We used the American College of Surgeons definition of surgery:

Surgery is performed for the purpose of structurally altering the human body by incision or destruction of tissues[...] Surgery also is the diagnostic or therapeutic treatment of conditions or disease processes by any instruments causing localized alteration or transportation of live human tissue, which include lasers, ultrasound, ionizing radiation, scalpels, probes, and needles. The tissue can be cut, burned, vaporized, frozen, sutured, probed, or manipulated by closed reduction for major dislocations and fractures, or otherwise altered by any mechanical, thermal, light-based, electromagnetic, or chemical means. All of these surgical procedures are invasive, including those that are performed with lasers, and the risks of any surgical intervention are not eliminated by using a light knife or laser in place of a metal knife or scalpel.[30]

We specifically excluded wound debridement using this definition and therefore excluded papers wherein this was the only procedure. We defined 'preventive HBOT' as HBOT used in a systematic way in the peri-operative period regardless of patient status in order to optimise recovery from surgery and/or avoid postoperative complications. We excluded the therapeutic use of HBOT for an established complication.

We included HBOT performed from the pre-operative period until 48 h after surgery. We accepted as a comparator either a sham HBOT procedure (the patient went into the chamber but did not actually receive an inspired oxygen pressure of >1.4 ATA) or usual care only with no specific additional therapy.

We included all studies measuring clinical patient outcomes measured at any time point from the intra-operative to postoperative period. We classified these outcomes according to the current standardised endpoints for peri-operative medicine[31]: *patient comfort* (e.g. postoperative nausea and vomiting, anxiety/stress, sleep quality), *clinical indicators* (e.g. peri-operative hypothermia, peri-operative iatrogenic injury, unplanned hospital readmission), *cognition and stroke* (e.g. stroke/transient ischemic attack, postoperative delirium/confusion, postoperative cognitive decline), *cardiovascular* (e.g. myocardial injury after noncardiac surgery, arrhythmias, hypotension), *respiratory* (e.g. pulmonary complications), *sepsis* (e.g. surgical site infection, bloodstream infection), *renal* (e.g. acute kidney injury), *bleeding and transfusion*, *organ failure and survival*, *cancer and long-term survival*, *patient-centered outcomes* (e.g. patient satisfaction, functional status, health-related quality of life) and *healthcare resource utilization* (e.g. length of stay).

We included all types of randomised controlled trials (RCTs, e.g. parallel, cross-over, cluster, factorial) with the caveat that they were published in English. We excluded conference abstracts.

Search strategy and information sources

The search strategy was developed by an experienced information specialist (AD) in close collaboration with the research team (Appendix 1, http://links.lww.com/EJA/A313). It was then reviewed by a second information specialist, following the Peer Review of Electronic Search Strategies (PRESS) guidelines.[32] The databases MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials were searched without language restrictions, from inception to 19 June 2018. The reference lists of included studies were also searched in addition to the online Database of Randomized Controlled Trials in Diving and Hyperbaric Medicine.[33] We also reviewed references of relevant book chapters[19,34] and consulted content experts for relevance and completeness.

Study selection

Identified studies were uploaded to a web-based systematic review software, DistillerSR (Evidence Partners, Ottawa, Ontario, Canada),[35] and double-hits were removed. A pilot screening tool was developed by the research team and piloted with 20 randomly selected articles (Appendix 2, http://links.lww.com/EJA/A314). This tool was iteratively refined until acceptable inter-rater reliability was established (minimum Kappa = 0.60). Two independent reviewers (LM, OCB) first assessed titles and abstracts for eligibility, followed by the full-texts of articles of included studies and those deemed 'unclear'. Screening for inclusion at each level was always conducted in duplicate, with disagreements resolved by consensus or involvement of a third reviewer as needed (SB, PL, MAM, MB, RP).

Data extraction

A data extraction form was developed and piloted, then used by the two independent reviewers (OCB, LM) to extract relevant information with DistillerSR.[35] Extracted data included publication details (e.g. first

author name, year of publication, country of data collection, funding, trial registration), study characteristics (e.g. study design, sample size, inclusion/exclusion criteria), patient demographics, intervention and comparator details, the type of surgical procedure and anaesthesia, and the effect of intervention on reported clinical outcomes. The data extraction form is given in Appendix 3, http://links.lww.com/EJA/A315.

Risk of bias

Two independent reviewers (OCB, LM) assessed each included study for risk of bias in six dimensions using the Cochrane collaboration's Risk of Bias tool.[14]

Data synthesis

A narrative synthesis of results was conducted. We planned to conduct a meta-analysis if appropriate.

Results

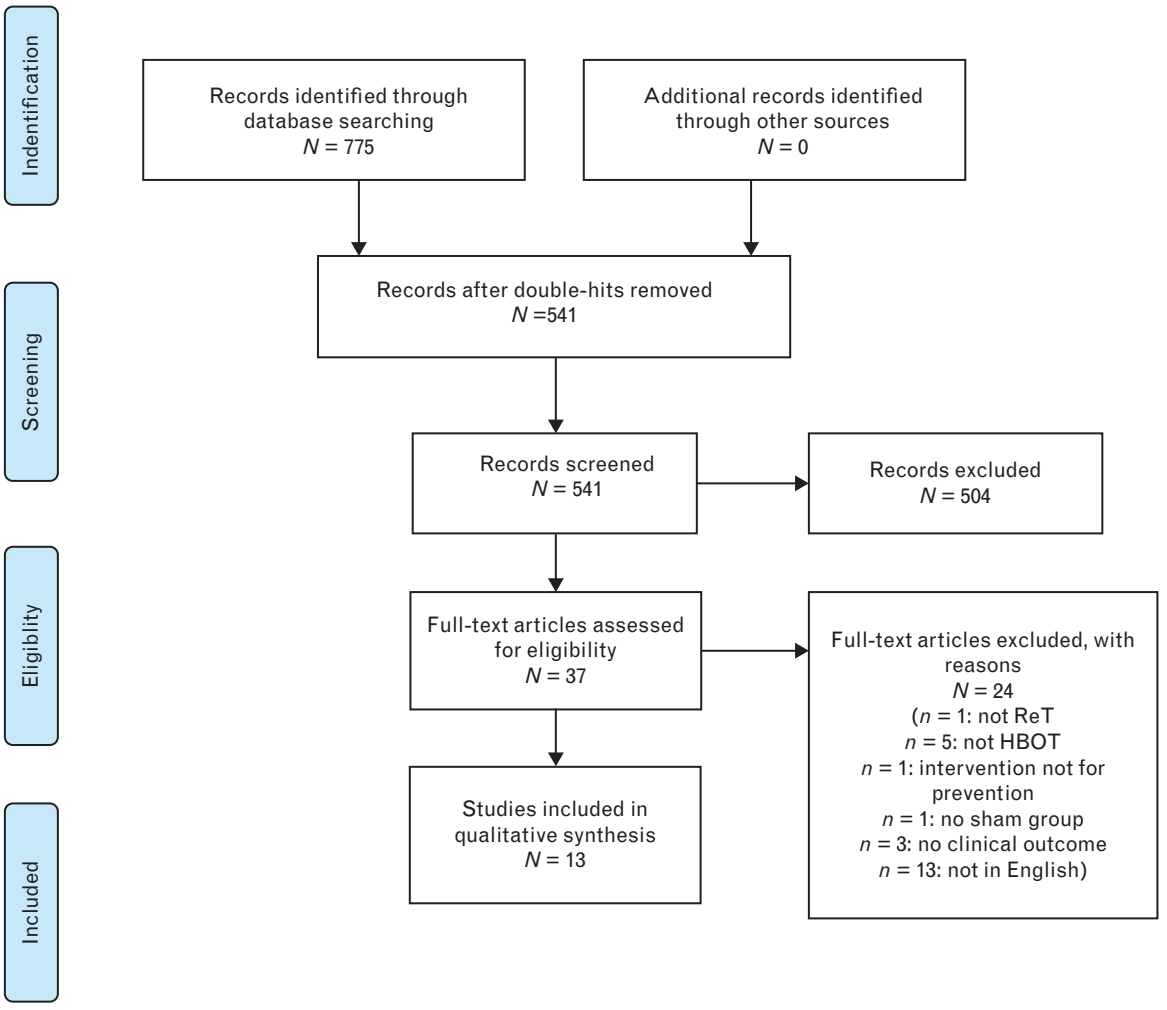
Study selection

The literature search yielded 775 studies. After removal of double-hits, 541 studies were assessed for eligibility (Fig. 1). Subsequently, 13 studies met the inclusion criteria and were included in this systematic review.

Study and patient characteristics

Details on included study and patient characteristics are provided in Table 1. Across the 13 studies, 627 participants were randomised to treatment and control groups (median = 45, range = 10 to 120). Included studies were published between 1967 and 2018, with the majority published after 2001 ($n = 10$). Twelve RCTs were single-centre [92.3%; $n = 553$ (88.2%)] and one was multicentre [$n = 74$ (11.8%)]. Types of surgery involved varied and included procedures such as coronary artery bypass surgery, tooth removal, orthopaedic surgery for crush

Fig. 1



PRISMA flow diagram.

Table 1 Study and patient characteristics (*n* studies = 13; *n* patients = 627)

Ref.	Single or multicentre RCT (*n* centres), *n* patients randomised	Type of surgery, Peri-operative phase of HBOT	Intended goal of HBOT	Type of chamber (mono or multiplace), Chamber Model Breathing break, Pressure, Duration (*n* sessions, frequency)	Comparator (sham vs. usual care); If sham: Type of chamber, Chamber Model, Breathing break, Pressure, Duration (n sessions, frequency)	Patient age (m/median, SD/range)	*n* (%) female	Patients prior radiation therapy (Y/N)	*n* (%) patients with diabetes
Bosco, 2014, Italy[22]	Single, 21	Pancreatico-duodenectomy, pre-operative	Preconditioning, modulation of the inflammatory response	Multiplace, NR, Two 5-min breaks, 2.5 ATA, 116 min (1)	Multiplace, NR, NR, 1.15 ATA NR	HBOT: M: 62.8 (11.1) F: 69 (3.3) Control: M: 62.6 (12.6) F: 72.2 (4.2)	HBOT: 50.0% Control: 63.6%	NR	NR
Bouachour, 1996, France[36]	Single, 36	Orthopaedic for limb crush injuries, postoperative	Wound healing for crush injuries	Multiplace, NR, NR, 2.5 ATA, 90 min (12; twice daily for 6 days)	Multiplace, NR, NR, ATA NR (12; twice daily for 6 days)	48.7 (18.6)	NR	NR	6 (16.7%)
Ersoz, 2016, Turkey[37]	Single, 22	Surgical treatment of sacrococcygeal pilonidal disease, postoperative	Would healing	NR, NR, Two 5-min breaks, 2.5 ATA, 90 min (18; 6 days per week for 3 weeks)	Usual care	28.5 (7.0)	0 (0%)	NR	NR
Li, 2011, China[26]	Single, 51	Coronary artery bypass graft surgery, pre-operative	Preconditioning, myocardial and cerebral protection	Monoplace, NR, One 5-min break, 2.0 ATA, 70 min (5, once daily day)	Usual care	62.1 (2.7)	0 (0%)	NR	17 (34.7%)
Marx, 1985, United States[38]	Multicentre (three centres), 74	Tooth (teeth) removal in irradiated segment of mandible, pre and postoperative	Soft tissue revascularisation	NR, NR, NR, 2.4 ATA, 90 min (20 pre-operatively, 10 postoperatively, all once daily, 5 or 6 days a week)	Usual care and antibiotics	NR	NR	Y	NR
Perrins, 1967, United Kingdom[39]	Single, 48	Plastic (split skin grafting), postoperative	Skin graft hypoxia correction	NR, Vicker's clinical transparent pressure chamber, NR, 2.0 ATA, 120 min (7, once day 1, then twice daily for 3 days)	Usual care	NR	NR	NR	NR
Schoen, 2007, Netherlands[45]	Single, 26	Head and neck oncology (tumour removal – various sites: tongue, mouth, mandible, oropharynx followed by radiation therapy), pre and postoperative	Soft tissue revascularisation, increased bone mineralisation and biomechanical forces	NR, NR, NR, 2.5 ATA, 80 min (20 pre-operatively, 10 postoperatively, NR)	Usual care	59.8 (7.5)	9 (34.6%)	Y	NR

Table 1 (*continued*)

Ref.	Single or multicentre RCT (*n* centres), *n* patients randomised	Type of surgery, Peri-operative phase of HBOT	Intended goal of HBOT	Type of chamber (mono or multiplace), Chamber Model Breathing break, Pressure, Duration (*n* sessions, frequency)	Comparator (sham vs. usual care); If sham: Type of chamber, Chamber Model, Breathing break, Pressure, Duration (n sessions, frequency)	Patient age (m/median, SD/range)	*n* (%) female	Patients prior radiation therapy (Y/N)	*n* (%) patients with diabetes
Sharifi, 2004, United States[40]	Single, 69	Percutaneous coronary interventions, pre and postoperative ($n=8$) OR postoperative ($n=16$)	Wound-healing process to reduce restenosis	Monoplace, Sechrist 2500 B Monoplace Hyperbaric System (Sechrist Industries, Anaheim, California), NR, 2.0 ATA, 120 min, two sessions within 18 h (2)	Usual care	64.2 (12.6)	26 (42.6%)	NR	18 (29.5%)
Tang, 2011, China[41]	Single, 120	Clipping of interacranial aneurysm, postoperative	Treatment of symptomatic cerebral vasospasm	Monoplace, NR, NR, 2.0 ATA, 60 min (at least 20, once daily)	Usual care	48 (29–76)	58 (48.3%)	NR	13 (8.7%)
Ueno, 2011, Japan[43]	Single, 45	Hepatectomy, postoperative	Oxygen delivery to tissues that is independent of fluid therapy or blood transfusions, to minimise requirement for peri-operative blood transfusions	Multiplace, Hyperbaric system NHC-408-A, K.K. Nakamura Tekko-Sho, Tokyo, Japan, NR, 2.0 ATM 60 min (2 or 3, at 3, 24 and 48 h if needed)	Usual care	64 (47–77)	NR	NR	14 (34.1%)
Vishwanath, 2011, India[44]	Single, 10	Free flap surgery: Free tissue transfer by microvascular technique, postoperative	Angiogenesis, reduction of congestion, resolution of oedema, immunomodulation, free flap survival	NR, NR, NR, 2.5 ATA, 60 min (7, once daily)	Usual care	Unclear (category range: 20 to 79)	Two (25%) (out of eight survival flaps)	NR	NR
Yogaratnam, 2010, United Kingdom[50]	Single, 81	Coronary artery bypass graft surgery, pre-operative	Preconditioning, improving myocardial left ventricular stroke work (LVSW)	NR, NR, One 5-min. break, 2.4 ATA, 100 min (1, 4 h prior to surgery)	Usual care	66.8 (NR)	19 (23.5%)	NR	8 (9.9%)
Yuan, 2011, China[27]	Single, 24	Posterior urethral reconstruction, postoperative	Angiogenesis, immune modulation, nerve regeneration to facilitate erectile function recovery	Multiplace, NR, NR, 2.0 ATA, 140 min (14, once daily)	Multiplace, NR, NR, 1.0 ATA, 140 min (14, once daily)	29.6 (7.2)	0 (0%), as per surgery definition	NR	0 (0%), as exclusion criterion

IC, intensive care unit; NR, not reported.

injuries, clipping of intracranial aneurysm and hepatectomy. Two studies recruited patients who had undergone prior radiation therapy [$n = 100$ (15.9%)]. Only six studies [46.2%; $n = 402$ (64.1%)] reported whether patients had diabetes. Across these studies, 76 patients (18.9%) were reported as diabetic.

Hyperbaric oxygen therapy intervention and control characteristics

HBOT was conducted pre-operatively only in three studies [$n = 153$ (24.4%)], postoperatively only in seven studies [$n = 305$ (48.6%)], and both pre and postoperatively in three studies [$n = 169$ (27%)].

The goal of peri-operative HBOT varied across studies and included treatment goals such as helping wound healing, myocardial and cerebral protection, and improved split skin graft survival. The number of HBOT treatments ranged from a minimum of one to a maximum of 30 (median = 7, IQR = 2 to 18) with a median pressure of 2.4 ATA (IQR = 2 to 2.5).

Among the included studies, HBOT was evaluated in comparison to usual care (i.e. no HBOT) in 10 studies [76.9%; $n = 546$ (87.1%)] and compared with sham HBOT in three studies [$n = 81$ (12.9%)]. Among the three studies that used sham HBOT, the chamber was pressurised to 1.0 ATA or 1.15 ATA. As specified in the Materials and methods section, we excluded studies that used a sham treatment with a pressure more than 1.4 ATA.

Effectiveness of hyperbaric oxygen therapy for preventing postoperative complications

Due to heterogeneity among the included studies, a meta-analysis could not be conducted. Outcome categories reported by each included study are summarised in Table 2. Clinical indicators (e.g. peri-operative iatrogenic injuries) were investigated most often [n studies = 8 (61.5%)] followed by patient-centred outcomes (e.g. satisfaction) [n studies = 5 (38.5%)].

Table 2 Outcomes reported by included studies (n studies = 13; n patients = 627)

StEP outcome category	Number of studies
Bleeding and transfusion	3
Cancer and long-term survival	1
Cardiovascular	3
Clinical indicators	8
Cognition and stroke	2
Healthcare resource utilisation	3
Organ failure and survival	4
Patient comfort	3
Patient-centred outcomes	5
Renal	1
Respiratory	3
Sepsis	2

StEP, Standardised Endpoints for Peri-operative Medicine.

Of the 13 included studies, 10 (76.9%) reported HBOT effectively improved at least one patient outcome [$n = 546$ (87.1%)],[22,26,27,36–42] while two (15.4%) found no effect of HBOT in any of the patient outcome assessed [$n = 55$ (8.8%)][43,44] and one found a negative effect of HBOT on patient outcome [$n = 26$ (4.1%)].[45] Details of the specific outcomes and effects for which the included studies found a positive effect of HBOT are provided in Table 3. Complete outcome data are provided in Appendix 4, http://links.lww.com/EJA/A316.

The three studies published before 2000 found a positive effect of HBOT on patient outcome (Fig. 2). Of the 10 studies published after 2001, one found a negative effect of HBOT on patient outcome and two reported no effect. The other seven reported a positive effect of HBOT on patient outcome. Three studies, one published before 2000 and two published afterwards, used a sham comparator (Tables 1 and 3).[27,36,46] Of the three studies with a sham comparator, two also featured a blinded procedure.[36,46]

For thoracic procedures, HBOT was reported to decrease ICU length of stay,[26] use of inotropic drugs,[26] late angina,[40] intra-operative blood loss,[42] and a composite of death, myocardial infarction, coronary artery bypass and revascularisation of target lesion for thoracic procedure.[40] In orthopaedic surgery, HBOT was reported to decrease the need for new surgical procedures,[36] the number of patients with osteoradionecrosis for dentistry surgery[38] and the number of sockets where osteoradionecrosis developed.[38] HBOT was reported to increase skin graft survival,[39] brain recovery[47] and erectile function/satisfaction[27] for plastic, ENT, neurologic and urologic procedures, respectively. It was also reported to decrease total epithelialisation time for colorectal surgery[48] and pulmonary complications for a general gastrointestinal procedure.[22]

Risk of bias

Overall, the studies included in this systematic review appear to be at a low or unclear risk of bias across the domains of sequence generation (selection bias), allocation concealment (selection bias), selective outcome reporting (reporting bias) and other sources of bias (Figs. 3 and 4). There were three studies at a high risk of bias for the domain blinding of participants and personnel (performance bias).[39,43,49] Two of these studies reported a positive effect of HBOT on surgical outcome,[39,49] while the third found no significant effect.[43] Three studies were at a high risk of bias for the domain incomplete outcome data (attrition bias).[40,45,50] Of these, two studies reported a positive effect of HBOT,[40,50] and one study reported a negative effect of HBOT on surgical outcome.[45] Only one study was at a high risk of bias for both random sequence generation (selection bias) and other sources of bias.[27] This study found a significant positive effect of HBOT on surgical outcome.

Table 3 Summary of results for studies reporting a significant effect for HBOT optimisation of surgical outcome

Ref.	Intervention and control group sample size	Outcome name, timing, primary or secondary outcome	Reported results
Bleeding and transfusion			
Yogaratnam, 2010[50]	HBOT group: $n=41$; Control group: $n=40$	Blood loss (ml), intra-operative, secondary	HBOT group ($n=41$): mean = 133 (range = 0 to 961) Control group ($n=40$): mean = ml (range = 0 to 152) $P=0.02$ (95% CI: -318 to -32)
Cardiovascular			
Li, 2011[26]	HBOT group: $n=14$; Control group: $n=15$	Use of inotropic drugs ($g\,kg^{-1}\,min^{-1}$), postoperative, secondary	HBOT group ($n=14$): mean = 6.9 ± 0.8 (24 h after ICU arrival) and 6.7 ± 0.8 (36 h after ICU arrival) Control group ($n=15$): mean = 10.2 ± 1.1 (24 h after ICU arrival) and 9.6 ± 1.1 (36 h after ICU arrival) $P<0.05$ (95% CI: NR)
Sharifi, 2004[40]	HBOT group: $n=24$; Control group: $n=37$	Late recurrence or worsening of anginal symptoms after 8 months, postoperative, secondary Revascularisation of target lesion, postoperative, secondary	HBOT group (n = 24): incidence = 0.04 Control group ($n=37$): incidence = 0.24 $P=0.001$ (95% CI: NR) HBOT group ($n=24$): incidence = 0 Control group ($n=37$): incidence = 0.22 $P<0.003$ (95% CI: NR)
Clinical indicators			
Bouachour, 1996[36]	HBOT group: $n=18$; Control group (Sham): $n=18$	Complete healing, postoperative, primary New surgical procedures, postoperative, primary	HBOT group ($n=18$): incidence = 0.94 Control group ($n=18$): incidence = 0.56 $P=0.009$ (95% CI: NR) HBOT group ($n=18$): incidence = 0.06 Control group ($n=18$): incidence = 0.33 $P=0.03$ (95% CI: NR)
Ersoz, 2016[37]	HBOT group: $n=10$; Control group: $n=12$	Complete epithelisation time of wounds (days), postoperative, primary	HBOT group: mean = 54 (range = 43 to 66) Control group: mean = 80 (range = 69 to 90) $P=0.003$ (95% CI: NR)
Marx, 1985[38]	HBOT group: $n=37$; Control group: $n=37$	Number of osteoradionecrotised sockets, postoperative, primary Number of patients with osteoradionecrosis, postoperative, primary	HBOT group: incidence = 0.11 Control group: incidence = 0.84 p value = NR (95% CI: NR) HBOT group: incidence = 0.05 Control group: incidence=0.30 P = NR (95% CI: NR)
Cognition and stroke			
Tang, 2011[41]	HBOT group: $n=60$; Control group: $n=60$	Glasgow Outcome Scale (assessment of brain recovery; score of 4 or 5), postoperative, primary Symptomatic cerebral vasospasm, postoperative, secondary	HBOT group: incidence = 0.90 Control group: incidence = 0.77 $P<0.05$, $x^2=6.03$ (95% CI: NR) Day 7: HBOT group: incidence = 0.43 Control group: incidence = 0.62 $P<0.05$ (95% CI: NR) Day 14: HBOT group: incidence = 0.08 Control group: incidence = 0.22 $P<0.05$ (95% CI: NR)
Healthcare resource utilisation			
Li, 2011[26]	HBOT group: $n=14$; Control group: $n=15$	ICU length of stay (h; for patients undergoing on-pump surgery), postoperative, secondary	HBOT group: mean = 59.4 ± 5.8 Control group: mean = 85.9 ± 10.8 $P<0.05$ (95% CI: NR)
Yogaratnam, 2010[50]	HBOT group: $n=41$; Control group: $n=40$	ICU length of stay (h), postoperative, secondary	HBOT group: mean = 21 (range = 6 to 28) Control group: mean = 26 (range = 21 to 76) $P=0.05$ (95% CI: 0.02 to 7.96)
Organ failure and survival			
Perrins, 1967[39]	HBOT group: $n=24$; Control group: $n=24$	Permanent graft survival, postoperative, primary	HBOT group: mean = 84.2% Control group: mean = 62.7% $P<0.01$; $t=2.92$ (95% CI: NR)

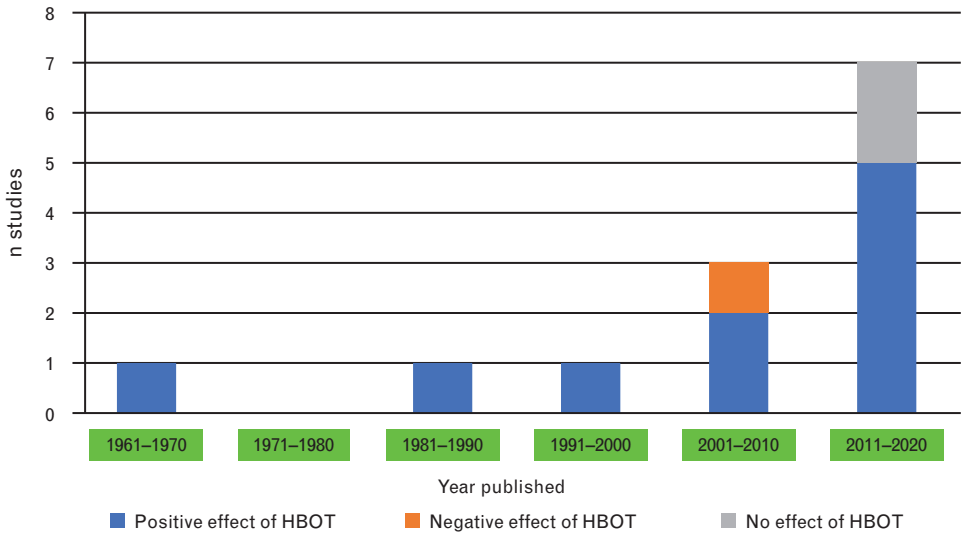
Table 3 (*continued*)

Ref.	Intervention and control group sample size	Outcome name, timing, primary or secondary outcome	Reported results
Sharifi, 2004[40]	HBOT group: $n=24$; Control group: $n=37$	Composite of death, myocardial infarction and need for target lesion vascularisation	HBOT group: incidence = 0.04 Control group: incidence = 0.35 $P=0.001$ (95% CI: NR)
Patient-centred outcomes			
Tang, 2011[41]	HBOT group: $n=60$; Control group: $n=60$	Functional state (Karnofsky Performance Scale), postoperative, secondary	HBOT group higher score than control group but values NR $P<0.05$; $t=3.94$ (95% CI: NR)
Yuan, 2011[27]	HBOT group: $n=12$; Control group (Sham): $n=12$	Total International Index of Erectile Function (IIEF) score, postoperative, NR Erectile function domain of IIEF score, postoperative NR Overall satisfaction domain of IIEF score, postoperative, NR Intercourse satisfaction domain of IIEF score, postoperative, NR IIEF-5 score (five-item version of IIEF), postoperative, NR	HBOT group: mean = 61.33 ± 4.05 Control group: mean = 52.43 ± 5.18 $P<0.001$ (95% CI: NR) HBOT group: mean = 23.75 ± 1.91 Control group: mean = 19.50 ± 2.88 $P=0.002$ (95% CI: NR) HBOT group: mean = 8.67 ± 0.49 Control group: mean = 7.17 ± 2.67 $P<0.001$ (95% CI: NR) HBOT group: mean = 11.92 ± 1.17 Control group: mean = 9.58 ± 1.56 $P=0.001$ (95% CI: NR) HBOT group: mean = 19.17 ± 1.70 Control group: mean = 15.67 ± 2.67 $P=0.002$ (95% CI: NR)
Respiratory			
Bosco, 2014[22]	HBOT group: $n=10$; Control group (Sham): $n=11$	Pulmonary complications, postoperative, secondary	HBOT group: incidence = 0 Control group: incidence = 0.55 $P=0.02$ (95% CI: NR)

CI, confidence interval; HBOT, hyperbaric oxygen therapy; NR, not reported.

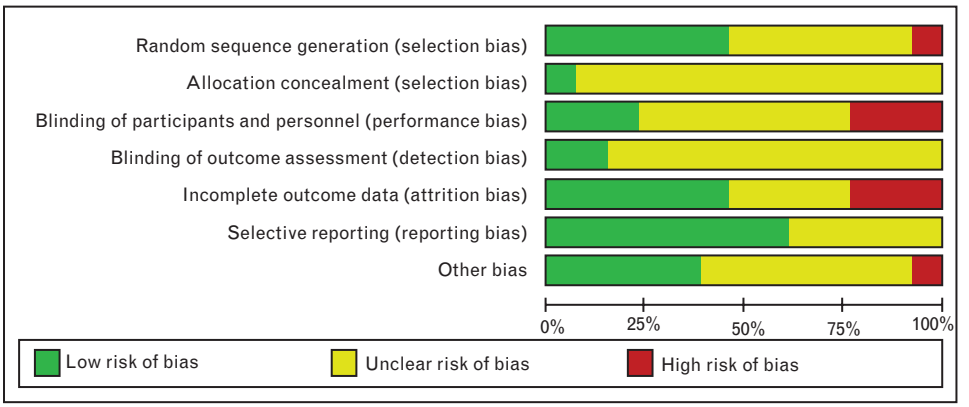
We observed that most studies did not report the funding source for their work or whether there were any conflicts of interest (Appendix 4, http://links.lww.com/EJA/A316). Among the four studies reporting their funding source, one was industry funded and found a positive effect of HBOT on clinical outcome. The remaining three studies were funded by an academic, governmental or health institution, of which two found a positive effect of HBOT on patient outcome while the third one was neutral. Only two studies reported whether or not there was a conflict of interest, with each declaring no conflict on behalf of the authors.

Fig. 2



Effect of hyperbaric oxygen therapy on surgical outcome by number of studies and year published. HBOT, hyperbaric oxygen therapy.

Fig. 3



Overall risk of bias.

Discussion

Despite being practiced for over 200 years, hyperbaric medicine has often been overlooked as a treatment option for optimising surgical patient outcomes. Ten out of 13 RCTs identified in this systematic review found that preventive HBOT in the peri-operative period improved at least one of the patient outcomes assessed. However, a wide range of heterogeneous patient outcomes were reported in the included studies and several other methodological limitations were observed, such as limited use of sham comparator and lack of blinding.

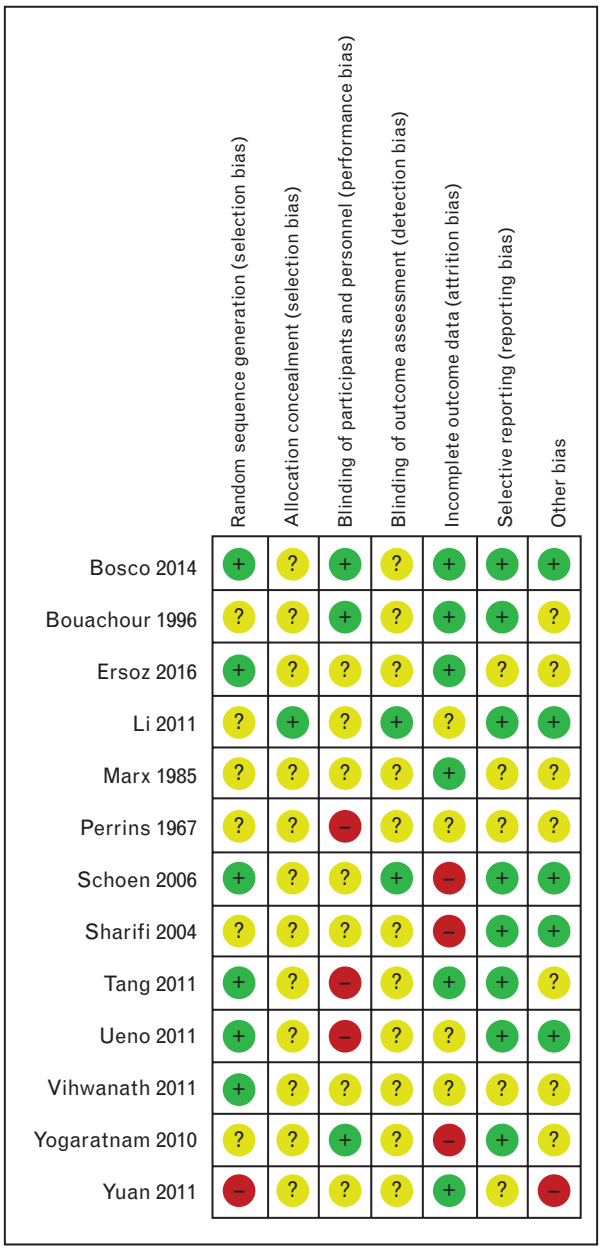
Some promising results were reported by several included RCTs across various types of surgery. Optimised surgical recovery demonstrated in the included RCTs is most likely a consequence of HBOT-induced anti-inflammatory and angiogenic effects. Although the anti-inflammatory effect has been demonstrated after a single HBOT, neovascularisation probably requires a series of at least five to seven daily sessions.[51–55] Accepted routine indications for HBOT includes patients with a history of radiation therapy and/or diabetes resulting in late radiation tissue injury and/or poor wound healing. These patients respond well to HBOT via neovascularisation.[34] Only two included RCTs enrolled patients with a history of radiation therapy and six included some patients with diabetes. On the basis of the known pathophysiology of HBOT, future studies may consider these two patient subgroups to optimise any HBOT effect on surgical patients.

We found three RCTs that specifically explored the preconditioning effect of HBOT. It has been demonstrated in both animal and human trials that exposure to high oxygen partial pressures can stimulate protective mechanisms against future hypoxic/ischemic stress through the same pathways historically used during hypoxic or hyperthermic preconditioning.[56] The mechanism involves the induction of HIF that binds to hypoxia response elements in target genes. HIF 1-alpha also induces vascular endothelial growth factor, erythropoietin and other genes that may be involved in protection against future injury. HIF, haemoxygenase and probably other inducible factors activate intracellular cascades, including kinases, transcription factors and changes in expression of multiple regulatory proteins.[57,58]

Although the effect of HBOT to *treat* postoperative complications has already been studied previously by others, the possible *preventive* effect of HBOT to optimise surgical outcome has rarely been considered. Our systematic review is further strengthened by the inclusion of RCTs only – the study design least likely subject to bias – and the examination of clinical outcomes as opposed to only biological or radiological assessments. Studies finding both positive, negative and no effects of HBOT were also published more recently, suggesting results are not skewed by advances in peri-operative care.

However, we found several methodological issues within the included RCTs. First, included studies were very heterogenous in terms of surgical context, timing, duration and mode of HBOT delivery, as well as outcome assessed. This heterogeneity prevented us from conducting any meta-analysis that may have led to practice recommendations. In particular, we found a wide range of heterogeneous clinical outcomes assessed in each included RCT. Similar methodological issues were pointed out and tackled in other fields, for example in anaesthesiology and perioperative medicine.[59] The proposed solution has been to standardise the definitions and use of outcome measures in clinical trials[60] and a number of initiatives have been underway in the last years to determine standardised core outcomes set.[59,61,62] Standardisation of core outcome set aims to reduce heterogeneity and ease knowledge synthesis while ensure relevant clinical outcomes. We would like to suggest that future work should consider standardising outcome of interest in hyperbaric medicine.

Fig. 4



Risk of bias for individual studies. green = low risk, yellow = intermediate risk or unclear, red = high risk.

Second, our findings also demonstrated that reporting within included RCTs was often suboptimal. For example, one RCT did not report treatment received by the control group. Several studies did not report the type of hyperbaric chamber (monoplace or multiplace), did not systematically report patients' radiation therapy history, which is well known to impact tissue healing, or did not report essential characteristics of the patient population such as sex.[63–65] Sex of patients may indeed be relevant in hyperbaric medicine. For example, Huijun *et al.* reviewed couples treated for carbon monoxide poisoning and analysed patient outcome according to sex and females' premenopausal or postmenopausal status. The authors concluded that 'sex is an important prognostic indicator in CO poisoning', as severity of poisoning and subsequent prognosis was worse for males relative to their female spouses. Although reporting issues are not unique to hyperbaric medicine, better attention to existing reporting guidelines is required to avoid research waste, particularly when considering the cost of studies in hyperbaric medicine. In addition to the standardised core outcomes set for HBOT indications proposed above, reporting guidelines tailored to hyperbaric medicine may help the research community to tackle these issues. Reporting guidelines may also specify that authors should report funding sources and conflicts of interest, as these were commonly not found within the included studies.

Other methodological weaknesses in included RCTs have been identified in this review. Only three RCTs used a sham comparator. Of these three, two were at a low risk of bias for blinding of participants and personnel, and all three studies concluded that there was a positive effect of HBOT on patient outcome. The conclusions of these studies strengthen our interpretation that preventive HBOT may be promising to optimise postoperative patient outcome. The small number of studies with a sham group and blinding may be due to the technical and logistical challenges in conducting such treatment in hyperbaric medicine. Also, we noted a variety of ways to conduct the sham, which suggests that there is no unanimously agreed upon 'best sham' for HBOT. Several of these methods have been recently reviewed and declared effective.[66] We excluded studies using sham treatment at a pressure greater than 1.4 ATA, as this may lead to a significantly increased partial pressure of oxygen.

Ten included RCTs did not blind patients, personnel or outcome assessors to treatment. Although it may lead to extra cost, blinding is both possible and desirable to reduce the risk of bias. The hyperbaric community may need to tackle these methodological challenges before being able to engage in large, well designed and reported multicentre RCTs.

All but one included RCTs were single centre and enrolled a modest number of patients. Future research in the field should consider conducting multicentre RCTs with larger samples for the promising interventions and surgical contexts identified in this review.

Despite all the methodological issues of the included RCTs described above, these should not take away from the need to conduct further research on peri-operative *preventive* HBOT given its potential benefits.

It should be acknowledged that there were 13 non-English papers excluded from this review. A recent report from the Agency for Healthcare Research and Quality

suggests that 'there remains a trade-off between completeness of systematic reviews (including all available studies) and risk of error (due to poor translation)'.[67] Google Translate was shown to be particularly inaccurate when translating Asian languages,[67] and many of the non-English studies identified by our literature search were from Asian countries. On the basis of the ratio of included to excluded papers in our review, it is also unlikely that many of these papers would have ultimately met our inclusion criteria after full-text review or significantly changed our findings.

Conclusion

Although limited in terms of both quantity and quality, there is some evidence to suggest that peri-operative *preventive* HBOT may be a promising intervention to improve surgical patient outcome. However, the HBOT literature relevant to this research question is heterogenous and limited by methodological issues that need to be addressed in the future. In particular, a sham group and blinded assessment of outcome should be considered for future studies along with a standardised core outcome set for hyperbaric medicine.

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