Support Care Cancer (2014) 22:1715–1726
DOI 10.1007/s00520-014-2198-z

REVIEW ARTICLE

Systematic review of hyperbaric oxygen therapy for the treatment of non-neurological soft tissue radiation-related injuries

Benjamin L. Hoggan · Alun L. Cameron

Received: 26 June 2013 / Accepted: 2 March 2014 / Published online: 29 March 2014

Abstract
Purpose The purpose of this paper was to provide an evidence-based evaluation of the safety and effectiveness of hyperbaric oxygen therapy (HBOT) for the treatment of non-neurological soft tissue radiation-related injuries (STRI).
Methods Systematic searches of medical bibliographic databases, the Internet, and lists of references were conducted in December 2010 and April 2013 to identify relevant primary studies. Inclusion and classification of papers was resolved through the application of a predetermined protocol. Information on both the safety and effectiveness of HBOT was analyzed.
Results Forty-one articles were included, with 11 comparing HBOT to a regimen without HBOT. Comparative evidence varied considerably in methodological quality, and numerous limitations were identified. Absolute data showed that serious adverse events after HBOT were rare, while more common adverse events were minor and self-limiting. Compared to observation, conventional, or sham therapies, evidence of benefit in clinical outcomes was shown for HBOT for radiation proctitis and wounds in irradiated soft tissue of the head and neck, but not for postirradiation soft tissue edema or radiation cystitis. Clinical outcomes differed little between HBOT and argon plasma coagulation for radiation proctitis and between HBOT and hyaluronic acid for radiation cystitis.
Conclusions HBOT is a safe intervention which may offer clinical benefits to patients suffering from radiation proctitis and non-neurological STRI of the head and neck. However, differing clinical responses across STRI demonstrate a need for further well-designed clinical trials to validate the use of HBOT for individual STRI, both as an adjunct to conventional treatments and relative to definitive treatments.

Keywords Hyperbaric oxygen · Radiation injury · Soft tissue · Radiotherapy · Systematic review

B. L. Hoggan · A. L. Cameron (✉)
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S), Royal Australasian College of Surgeons, 199 Ward Street, North Adelaide 5006, SA, Australia
e-mail: alun.cameron@surgeons.org

Introduction

Radiotherapy is a common and well-established treatment of malignancies across a variety of anatomical areas. However, anatomical structures surrounding a cancer, such as soft tissue, are also irradiated during the course of therapy. Radiotherapy is associated with a broad spectrum of normal tissue reactions, and it is impossible to cure a tumor by radiotherapy without risk of injury to normal tissues [1, 2]. One potential consequence of radiotherapy is serious soft tissue radiation-related injury (STRI) that can develop months or years posttreatment [2–4]. When an STRI occurs, soft tissues undergo deterioration in microvascularity with accompanying fibrosis, a process which continues until there is insufficient oxygenation to maintain tissue integrity and normal function. Damage may eventually reach a critical point where tissue breaks down and an ulcer or area of radionecrosis results. This process can be exacerbated by secondary damage from infection or surgery in the affected area, even long after irradiation [2]. The effects of STRI are progressive and do not spontaneously reverse [5–7].

While the pathological processes of STRI are similar throughout the body, some tissues appear more susceptible to injury than others. The pelvis, particularly the rectum, and the skin and mucosa of the head and neck region are especially sensitive [2]. While estimates vary, review articles have reported STRI incidence rates ranging from 3 to 18 % across a range of anatomical areas. This includes rectal complications following prostate brachytherapy [4], complications following

radiotherapy of gynecological malignancies [8], and damage to the mouth and mandible following brachytherapy for head and neck cancer [9].

It has been proposed that the enhanced oxygen delivery offered by hyperbaric oxygen therapy (HBOT) may prevent breakdown of irradiated tissue, promote healing, and improve tissue quality where healing processes are otherwise inhibited by insufficient oxygen supply [10]. Although minor variations in clinical practice occur, HBOT commonly involves patients inhaling 100 % oxygen via face mask, head tent, or endotracheal tube while inside a treatment chamber pressurized at 2 to 2.5 atmosphere absolute (ATA) [11]. Sessions are generally 60 to 120 min in duration, delivered up to twice daily for approximately 30 to 60 sessions, depending on patient response. Experimental and clinical studies have indicated that HBOT can reverse the histopathological changes of STRI, improving vascularity and inducing fibroplasia and angiogenesis in irradiated tissue [6, 12, 13]. However, neurological tissue appears resistant to HBOT and is generally not considered appropriate for treatment [10, 14, 15].

Although HBOT has been utilized for the treatment of STRI for many years, previous health technology assessments and systematic reviews have questioned the quality of evidence supporting its clinical effectiveness [16–21, 15, 22, 23]. However, since 2007 there has been an increase in the number and quality of comparative studies published, to the point a recent Cochrane review of randomized controlled trial (RCT) evidence concluded that HBOT is associated with improved outcomes for people with STRI of the head, neck, anus, and rectum [10].

The current paper is an updated précis of a systematic review assessing HBOT for the treatment of non-neurological STRI and chronic nondiabetic wounds, commissioned to inform public funding considerations within the context of the Australian healthcare system [24]. It presents only results relating to non-neurological STRI, and has been revised to incorporate evidence published subsequent to the original review. It expands on the aforementioned Cochrane review by additionally including relevant non-RCT evidence.

Methods

Search strategy

A review protocol was developed with input and approval from an advisory panel that included clinical experts on HBOT [24]. The search strategy was developed for maximum comprehensiveness, and is detailed in the original review [24]. The strategy incorporated a combination of text terms and subject headings relating to STRI and HBOT (Table 1) derived from previous systematic reviews of HBOT and clinical expert advice. Due to the requirements of the original review, the original strategy also incorporated terms relating to nondiabetic wounds.

Table 1 Search terms applied

Area of enquiry	Search terms
Non-neurological soft tissue radiation injuries	Subject headings
	Radiotherapy
	Text words
	radiation*, radiotherap*, damage*, injur*, wound*, destruction, necrosis, edema, oedema, proctitis, enteritis, cystitis, radionecrosis
Hyperbaric oxygen therapy	Subject headings
	Hyperbaric oxygenation
	Text words
	hyperbar*, high pressure, oxygen*, HBO*, multiplace chamber, monoplace chamber

A systematic search of electronic databases (CINAHL, the Cochrane Library, Embase, PubMed, University of York Center for Reviews and Dissemination) was conducted in December 2010 and updated in April 2013. Database searches were augmented with searches of registers of research and clinical trials, health technology assessment (HTA) websites, and bibliographies of retrieved articles. The searches were conducted without language restrictions. The updated search did not employ the terms relating to nondiabetic wounds. The lead author conducted the search, retrieval, and selection process, with advice provided by the second author in case of any uncertainty regarding study suitability. Where needed, clinical expert feedback was used to advise or confirm any remaining issues regarding study selection.

Study inclusion and exclusion criteria

Studies were included if clinical data relating to patients with preexisting non-neurological STRI could be extracted. Per clinical expert opinion and to reflect standard clinical practices, HBOT was defined as exposure to 100 % oxygen at ≥1.5 ATM for at least 60 min in an appropriate hyperbaric chamber. RCTs, other controlled or comparative studies, and experimental studies were all considered for inclusion. Any study that directly compared HBOT to a regimen not using HBOT (e.g., observation, definitive treatments, conventional treatments, and sham procedures) was considered for the assessment of safety and effectiveness. Any noncomparative study (e.g., case series) was considered for the assessment of safety alone, and was only included if it reported adverse event occurrence. Noncomparative studies were restricted to studies where enrolment was consecutive, or the study included all patients treated within a specified time period. Foreign

language articles were excluded unless they provided a level of evidence at least equivalent to the highest level English-language evidence. In the case of clear duplicate publications, the latest and most complete article was included.

Outcomes assessed

Safety was assessed through adverse events including mortality, decompression illness, oxygen toxicity, barotrauma, myopia, and claustrophobia. Clinical outcomes of interest for assessing effectiveness included rates of healing, time to healing, symptom reduction, radiation-induced morbidity, and quality of life.

Data extraction and synthesis

Data were extracted by the lead author using extraction tables in which all relevant study information could be included in a tabulated and standardized manner. Each table was compared for accuracy against the original paper by a second researcher. Included studies were allocated a level of evidence as defined by the National Health and Medical Research Council [25], while all comparative studies, both randomized and nonrandomized, were critically assessed for quality according to the Cochrane reviewers' handbook [26] and CONSORT statement [27].

Where possible, descriptive statistics were extracted or calculated for each safety and effectiveness outcome, with a qualitative synthesis of the results performed. Due to considerable variation across studies with regards to STRI, methodology, outcomes reported, and duration of and losses to follow-up, meta-analysis was not possible.

Results

Description of studies

A total of 41 articles were included for assessment (Fig. 1). This included seven articles reporting six separate RCTs [28–30, 13, 31–33]; the results of one RCT were reported within two articles [32, 33]. Four nonrandomized comparative studies were also included [34–37]. The remaining 30 studies were noncomparative, employing HBOT alone [38–67].

Details of included comparative studies are provided in Table 2. Treated STRI included radiation proctitis [34, 28, 32, 33], irradiated soft tissues of the head and neck [30, 13, 37], radiation cystitis [36, 31], and postirradiation soft tissue edema [35, 29]. Treatment protocols involved HBOT at 2.0 to 2.5 ATA, with sessions 60 to 100 min in duration. While two comparative studies failed to report the HBOT protocol employed [30, 32, 33], both had been included in the recent Cochrane review [10], and were included in the present review on clinical expert advice. The majority of studies compared HBOT to observation or variously-defined conventional treatments without HBOT, although sham treatment [28], intravesical instillation of hyaluronic acid [31], and argon plasma coagulation (APC) [34] were also employed.

Methodology of included studies

The methodological quality of the included comparative evidence varied considerably, and numerous limitations were identified. Only one comparative study reported power calculations [29], and only two included more than 40 patients per treatment arm [28, 30]. Two comparative studies did not

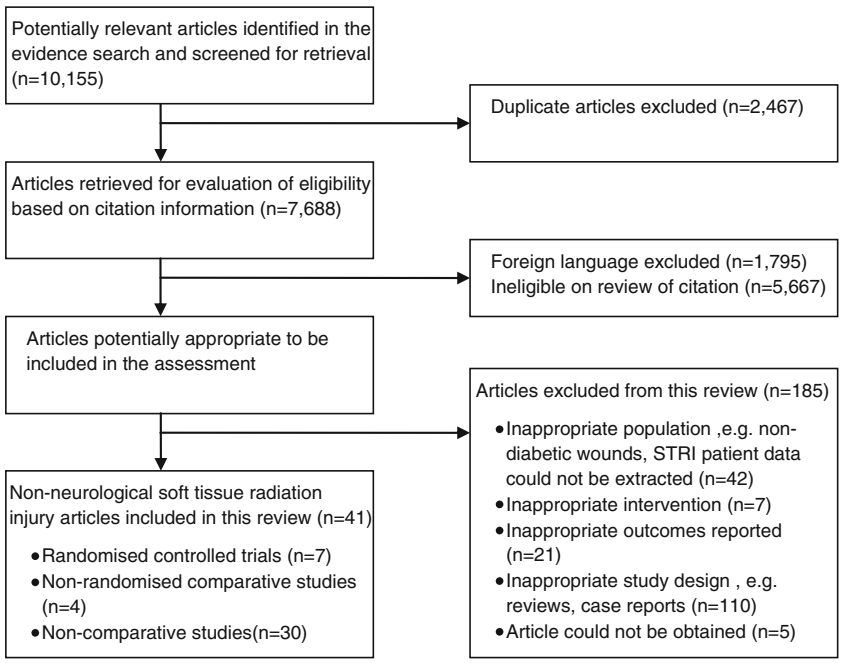

Fig. 1 Flowchart demonstrating the selection of articles

Table 2 Summary of comparative studies included for assessment

Reference	*n*	Study design	HBOT intervention	Comparator	Study methodology	Follow-up	Outcome measures
Radiation proctitis							
Álvaro-Villegas 2011 [34]	31	Prospective, nonrandomized HBOT: 17 Comparator: 14	2.0–2.5 ATA, 90 min Mean 35±5 (SD) sessions	Noncontact APC, 2.3 mm diameter catheter, 1.6 L/min flow rate at 60 W Mean 3±1 (SD) sessions	Comparability of groups: no selection apparent, groups comparable across demographic and clinical characteristics Allocation concealment: no attempt at concealment reported Blinding: no attempt at blinding reported Outcome reporting: moderately well reported; outcomes provided for all patients (no losses to follow-up noted)	3 months	Resolution of bleeding Radiation-induced morbidity (LENT-SOMA) Hemoglobin levels Transfusions required
Clarke 2008 [28]	150	Multicenter RCT HBOT: 76 Comparator: 74	2.0 ATA, 90 min 30 or 40 sessions (5 per week)	Sham treatment (air breathing at 1.1 ATA, 90 min) 30 or 40 sessions (5 per week)	Randomization process: Clearly stated and appropriate Allocation concealment: concealed from patients and investigators Blinding: patients and outcome assessors both blinded Outcome reporting: well reported; significant number of patients did not complete treatment, outcomes provided for all patients, intention-to-treat analysis conducted, but no QoL results presented	Outcomes recorded immediately posttreatment	Healing or improvement of proctitis Radiation-induced morbidity (LENT-SOMA) QoL assessment (EPIC, SF-12)
Sidik 2007 [32, 33]	65	RCT HBOT: 32 Comparator: 33	HBOT protocol not reported Minimum 18 sessions	Described as "symptomatic treatment"	Randomization process: little detail provided Allocation concealment: no attempt at concealment reported Blinding: no attempt at blinding reported Outcome reporting: poorly reported; significant losses to follow-up, not all patient outcomes provided	6 months	Healing of proctitis Radiation-induced morbidity (LENT-SOMA) QoL assessment (Karnofsky score)
Radiation cystitis							
Shao 2012 [31]	36	RCT HBOT: 20 Comparator: 16	2.5 ATA, 60 min 30 sessions (7 per week)	Intravesical hyaluronic acid instillation, 40 mg weekly in the first month then monthly over the following 2 months	Randomization process: little detail provided Allocation concealment: no attempt at concealment reported Blinding: no attempt at blinding reported Outcome reporting: moderately well reported; outcomes provided for all patients (no losses to follow-up noted)	18 months	Complete or partial resolution of cystitis Bladder voiding frequency Pelvic pain
Mohamad Al-Ali 2010 [36]	14	Retrospective, nonrandomized HBOT: 10 Comparator: 4	2.5 ATA, 60 min 30 sessions (7 per week)	Observation with no further treatment	Comparability of groups: discrepancies likely exist in demographic and clinical characteristics Allocation concealment: no attempt at concealment reported	Mean 18 months; range 1–6 years	Resolution of bleeding

Table 2 (continued)

Reference	*n*	Study design	HBOT intervention	Comparator	Study methodology	Follow-up	Outcome measures
					Blinding: no attempt at blinding reported Outcome reporting: moderately well reported; outcomes provided for all patients (no losses to follow-up noted)		
Wounds in irradiated soft tissue of the head and neck region							
Marx 1999 [30]	160	RCT HBOT: 80 Comparator: 80	HBOT protocol not reported 20 presurgery sessions, 10 postsurgery sessions	Control group treated with surgery without HBOT	Randomization process: no detail provided; no information reported on comparability of groups at baseline Allocation concealment: no attempt at concealment reported Blinding: no attempt at blinding reported Outcome reporting: poorly reported; all patient outcomes provided, but potentially from differing periods of follow-up	Not reported	Wound infection Wound dehiscence Delayed healing
Marx 1985 [13]	74	Multicentre RCT HBOT: 37 Comparator: 37	2.4 ATA, 90 min 20 sessions preextraction, 10 sessions postextraction (5 or 6 per week)	Standard tooth extraction, with 1 million units aqueous penicillin G before surgery, 500 mg phenoxymethyl penicillin four times daily for 10 days after surgery	Randomization process: no detail provided; no information reported on comparability of groups at baseline Allocation concealment: no attempt at concealment reported Blinding: no attempt at blinding reported Outcome reporting: moderately well reported; outcomes provided for all patients (no losses to follow-up noted)	6 months	Healing of dental extraction socket wounds
Neovius 1997 [37]	30	Retrospective, nonrandomized with historical control HBOT: 15 Comparator: 15	2.47 ATA, 75 min Mean 31 sessions postsurgery, range 20-42	Historical control group treated with surgery without HBOT	Comparability of groups: criteria for selection of historical control group not reported; discrepancies may exist in demographic and clinical characteristics Allocation concealment: no attempt at concealment reported Blinding: no attempt at blinding reported Outcome reporting: well reported; all patient outcomes provided	Until healing; range 1–6 months	Healing of wounds
Soft tissue edema following irradiation for breast cancer							
Carl 2001 [35]	44	Prospective, nonrandomized HBOT: 32 Comparator: 12	2.37 ATA, 90 min Median 25 sessions, range 7–60 (5 per week)	Observation with no further treatment	Comparability of groups: comparator group was patients who refused HBOT; little information reported on comparability of groups at baseline Allocation concealment: no attempt at concealment reported Blinding: no attempt at blinding reported Outcome reporting: moderately well reported; outcomes provided for all patients (no losses to follow-up noted)	HBOT: median 11 months; range 1–32 Comparator: median 7 months; range 2–38	Resolution of symptoms Radiation-induced morbidity (LENT-SOMA)

Table 2 (continued)

Reference	*n*	Study design	HBOT intervention	Comparator	Study methodology	Follow-up	Outcome measures
Gothard 2010 [29]	58	Multicentre RCT HBOT: 38 Comparator: 20	2.4 ATA, 100 min 30 sessions (5 per week)	Best standard care without HBOT	Randomization process: clearly stated and appropriate Allocation concealment: concealed from patients and investigators Blinding: no attempt at blinding reported Outcome reporting: well reported; all patient outcomes provided, but no QoL results presented	12 months	Change in arm volume QoL assessment (lymphedema QoL scale, SF-36)

APC argon plasma coagulation, *ATA* atmosphere absolute, *EPIC* expanded prostate cancer index composite, *HBOT* hyperbaric oxygen therapy, *LENT-SOMA* late effects normal tissues - subjective, objective, management, analytic scale, *QoL* quality of life, *RCT* randomized controlled trial, *SD* standard deviation, *SF-12* short form-12 health survey, *SF-36* short form-36 health survey

report patient inclusion or exclusion criteria [30, 37], and three reported little or no information regarding patient baseline characteristics [35, 30, 13]. Four studies reported comparative outcomes more than 6 months after treatment [35, 29, 36, 31]. Where reported, completeness of follow-up ranged from 61.3 to 100 % of patients. Only one comparative study reported analyses on an intention-to-treat basis [28].

With regards to evidence from randomized trials, two RCTs did not report randomization procedures employed [30, 13]. Only two RCTs described randomization procedures in detail [28, 29]. These were also the only RCTs to report concealment of treatment allocation, with the RCT comparing HBOT to sham treatment employing a double-blind methodology [28]. Although the remaining RCTs utilized comparator treatments that were considerably different to HBOT, none reported blinding outcome assessors to patient treatment allocation. One RCT was published as a book chapter, and the peer-review process to which it was subject is uncertain [30]. In two RCTs where it was suggested that some quality of life outcomes did not favor HBOT, detailed results were not reported [28, 29].

Among noncomparative studies, populations were small, with only 10 studies reporting more than 20 patients with STRI [40–42, 44, 49, 52, 54, 59, 62, 63]. Follow-up length varied, but was greater than 12 months in most of these studies. Most noncomparative studies did not conduct or report patient follow-up at uniform time points.

Safety

Seventeen studies comprising of 468 patients reported on occurrence of patient mortality during follow-up [38, 40, 41, 28, 43–46, 50, 55, 56, 58, 60, 32, 33, 63, 64, 66]. While a total of 69 mortalities were reported across these studies (14.7 %), no mortalities were attributed to HBOT. Where stated, mortalities occurred well after HBOT and were due to recurrence or progression of malignancy, progression of STRI after treatment failure, or other causes unrelated to HBOT.

A total of 29 studies comprising of 700 patients reported details of nonfatal adverse events associated with HBOT (Table 3) [38–40, 35, 41, 28, 42, 45–48, 29, 51–55, 36, 37, 57–65, 67]. Serious adverse events associated with HBOT were rare. Oxygen toxicity of the central nervous system (CNS), manifesting most commonly as seizures or convulsions, was reported in 11 studies [38, 41, 28, 42, 47, 48, 53, 54, 37, 57, 67], occurring in 1.7 % of patients within those studies, and 0.9 % of patients across all studies reporting adverse events. No other potentially serious adverse events (e.g., pulmonary edema, pneumothorax, arterial gas embolism, and pulmonary oxygen toxicity) were reported.

The most common adverse events associated with HBOT were ear barotrauma and oxygen-induced vision changes. These were generally transient and resolved without

Table 3 Summary of HBOT-related adverse events reported by all studies included for assessment

Adverse event	Studies	Patients *N*	Incidence *n*	Rate where reported (%)	Rate across total number of patients (%)
Ear barotrauma[a]	18	510	77	15.1	11.1
Vision change[b]	10	343	44	12.8	6.3
Claustrophobia/anxiety	5	176	9	5.1	1.3
CNS oxygen toxicity[c]	11	343	6	1.7	0.9
Sinus barotrauma	1	120	1	0.8	0.1
Hemoptysis	1	32	1	3.1	0.1
Angina episode	1	18	1	5.6	0.1
Exacerbation of aminodarone-induced pulmonary fibrosis	1	10	1	10.0	0.1
Hypertension	1	9	1	11.1	0.1
No adverse events related to HBOT	7	134			
Total	29	700			

CNS central nervous system, *HBOT* hyperbaric oxygen therapy

[a] Includes patients reporting significant ear equalization problems, or requiring myringotomy and/or tympanostomy tubes

[b] Includes any mention of "vision change" or "myopia"; description of severity of vision changes included "transient" and "significant"

[c] Includes patients described as experiencing "oxygen toxicity seizure," "hyperbaric oxygen-induced seizure," "tonic-clonic seizure," and "convulsions"

intervention, and rarely required cessation of HBOT. Ear barotrauma, which for purposes of the current review included patients with ear equalization problems or requiring myringotomy and/or tympanostomy tubes, was reported in 18 studies [41, 28, 42, 46, 47, 29, 51, 53–55, 37, 57–59, 62, 64, 65, 67], occurring in 15.1 % of patients within those studies and 11.1 % of patients across all studies reporting adverse events. Vision change and myopia was reported in ten studies [28, 42, 45, 46, 48, 29, 52, 54, 57, 65], occurring in 12.8 % of patients within those studies and 6.3 % of patients across all studies reporting adverse events. Claustrophobia or anxiety in the treatment chamber was reported in five studies [28, 46, 48, 37, 57], occurring in 5.1 % of patients within those studies and 1.3 % of patients across all studies reporting adverse events. Seven studies comprising of 134 patients explicitly stated that no adverse events associated with HBOT occurred [39, 40, 35, 36, 60, 61, 63].

An additional single-center case series of 525 patients, of which 463 had STRI and met the inclusion criteria for this review, found CNS oxygen toxicity manifested as seizure in two patients (0.4 %), temporary tympanostomy tube placement was necessary in approximately 5 % of patients, and approximately 11 % of patients experienced symptomatic oxygen-induced myopia [49]. This study was not incorporated into Table 3 as explicit patient numbers were not provided for all adverse events.

Comparative studies

One RCT found incidence of urinary tract infection at 6-month follow-up was greater in patients who received hyaluronic acid for radiation cystitis than those who received HBOT (42.8 vs. 10 %, p=0.034), which was attributed to repeated urethral catheterization [31]. This difference was nonsignificant at 12- and 18-month follow-up.

No other comparative studies provided a comparison of adverse events for HBOT and comparator patient groups. One nonrandomized comparative study noted that 5 of 14 patients (35.7 %) experienced minor complications of rectal pain and ulcer after receiving APC for radiation proctitis, but did not report adverse events for HBOT patients [34]. Five studies reported adverse event data for HBOT only [35, 28, 29, 36, 37]; this data was incorporated into Table 3.

Effectiveness

Given the diversity in STRI treated and resultant differences in clinical outcomes reported, results relating to the effectiveness of HBOT are presented separately for each STRI.

Radiation proctitis

Two RCTs [28, 32, 33] and one nonrandomized comparative study [34] examined HBOT for treatment of radiation proctitis. A well-designed RCT comparing HBOT to sham treatment reported that a significantly greater proportion of HBOT patients demonstrated at least "moderate" healing of proctitis immediately after completion of treatment (87.5 vs. 62.5 %, p=0.0009) [28]. Although a considerable number of patients in both groups failed to complete treatment, this benefit held true in intention-to-treat analyses. A small number of HBOT patients experienced complete healing of proctitis (7.8 %), while no patient in the sham treatment group experienced complete healing (no statistical analysis

reported). The second RCT reported that treatment with HBOT significantly decreased the prevalence of radiation proctitis compared to symptomatic treatment alone at 6-month follow-up (76.9 vs. 42.9 %, $p=0.026$), although a considerable number of patients had been lost to follow-up [33]. The nonrandomized comparative study found HBOT patients required statistically more blood transfusions than APC patients at 1-month (3.4 vs. 0.6, $p=0.03$) and 2-month follow-up (2.5 vs. 0.7, $p=0.04$) [34]. This difference was nonsignificant after 3 months. By the end of follow-up, the study found no difference between groups with regards to the number of patients with persistent rectal bleeding.

All three comparative studies reported radiation-induced morbidity using the late effects normal tissues-subjective, objective, management, and analytic (LENT-SOMA) scale. The well-designed RCT reported that HBOT and sham treatment patients both experienced statistically significant improvements (i.e., reductions) in LENT-SOMA score from baseline levels immediately following treatment ($p<0.0001$) [28]. HBOT patients reported significantly lower LENT-SOMA scores ($p=0.0150$) than patients receiving sham treatment, indicating greater improvement following HBOT. The second RCT reported LENT-SOMA scores improved significantly more after HBOT than symptomatic treatment at 2-month ($p<0.001$) and 6-month follow-up ($p=0.008$) [32]. The nonrandomized comparative study found HBOT patients reported significantly lower LENT-SOMA scores than APC patients at 1-month ($p=0.01$) and 2-month follow-up ($p=0.03$) [34]. The difference was nonsignificant after 3 months.

With regards to quality of life measures, the well-designed RCT found HBOT patients experienced a statistically significant improvement on the "bowel bother" subscale of the expanded prostate cancer index composite (EPIC) immediately after treatment (14.1 %, $p=0.0007$), while sham patients did not (5.8 %, $p=0.1521$) [28]. However, no between-groups statistical comparison was reported, and HBOT patients were reported as having worse subscale scores at entry to the trial. No differences between groups were reported for the EPIC "bowel function" subscale or the Short Form-12 health survey. The second RCT reported significantly greater improvement in Karnofsky score among HBOT patients than those receiving symptomatic treatment at 2-month ($p<0.001$) and 6-month follow-up ($p=0.007$) [32].

Radiation cystitis

An RCT comparing HBOT to instillation of hyaluronic acid found no statistical difference between treatment groups in resolution of cystitis or degree of self-reported pain through 18 months of follow-up [31]. Hyaluronic acid patients experienced a greater reduction in frequency of bladder voiding than HBOT patients at 12-month follow-up ($p=0.002$), but no difference was found at 6- or 18-month follow-up. A small retrospective nonrandomized study found the cure rate of radiation cystitis in HBOT patients to actually be lower than the rate of spontaneous resolution observed in a control group without HBOT, although the difference was not statistically significant [36]. Findings from this study were potentially confounded by HBOT patients being considerably older than those in other comparative studies, and patients being allocated to the control group if they were physically unfit to undergo HBOT.

Wounds in irradiated soft tissue of the head and neck region

Two RCTs [30, 13] and one nonrandomized comparative study [37] examined HBOT for the treatment of wounds in irradiated soft tissue of the head and neck. An RCT examining patients who had soft tissue flaps surgically introduced into irradiated tissue reported that patients who underwent HBOT before and after surgery were significantly less likely to develop wound infections ($p=0.0019$), wound dehiscence ($p<0.0001$), and delayed wound healing ($p<0.0001$) than patients who did not receive HBOT [30]. The second RCT compared pre- and posttreatment HBOT to penicillin for the treatment of socket wounds after dental extractions from irradiated soft tissue [13]. At 6-month follow-up, significantly more socket wounds had healed in HBOT patients (97.4 vs. 77.4 %, $p<0.0001$), and significantly more HBOT patients had healing of all socket wounds (94.6 vs. 70.3 %, $p=0.006$). A retrospective nonrandomized study that examined the healing of wound complications following surgery in irradiated soft tissue of the head and neck found that 80.0 % of HBOT patients had complete healing of their wound after 5 months, compared to 46.7 % of patients in the control group treated without HBOT [37]. This difference neared statistical significance ($p=0.06$).

Soft tissue edema following irradiation for breast cancer

A well-designed RCT that compared patients receiving HBOT adjunctive to standard treatment to patients receiving standard treatment alone reported no statistically significant differences in improvement of arm lymphedema, related physiological response measures, or patient quality of life at 12-month follow-up [29]. A nonrandomized study comparing HBOT to an observational control group utilized a modified LENT-SOMA scale, reporting significantly greater improvements in levels of pain, edema, and erythema of the chest wall ($p<0.001$) in HBOT patients [35]. Differences were not seen for tissue fibrosis or telangiectasia, although both groups had very low baseline scores on these measures.

Discussion

HBOT has long been used for the treatment of STRI, with the earliest study included in this review dating back to 1976 [50].

However, previous health technology assessments and systematic reviews have consistently questioned the utility of the available clinical evidence. Some concluded that the paucity of high-quality evidence precluded the effectiveness of HBOT from being definitively established [16–21, 15, 22, 23]. Others have offered tentative support for the treatment of specific STRI, based on lower-grade evidence such as noncomparative case series [68, 69, 14, 70, 71, 1, 11].

A recent Cochrane review concluded that HBOT is associated with improved outcomes for people with STRI of the head, neck, anus, and rectum [10]. Although the Cochrane review included 11 RCTs, it examined late radiation injuries to all tissues, including neurological tissues and osteoradionecrosis. The current review included the five pertinent RCTs from the Cochrane review, additional published data from one RCT [33], and one RCT published subsequent to the Cochrane review [31]. It also included 4 nonrandomized comparative studies to further inform the assessment of clinical safety and effectiveness, and 30 noncomparative studies to assess the occurrence of adverse events.

Despite a recent increase in comparative studies published, the current systematic review once again highlights the limitations of the available evidence justifying the use of HBOT for non-neurological STRI. The methodology of comparative studies, including RCTs, was generally of moderate to low quality, or could not be verified. The majority had small patient populations, and it is unclear whether they were adequately powered. The comparative studies also commonly reported short follow-up periods. This raises concerns regarding the durability of the results, given that longer-term outcomes were generally less favorable for HBOT, and that some studies have shown potential for STRI recurrence after initially successful HBOT [72, 73, 28, 45, 41]. While it is acknowledged that blinding patients to treatment allocation poses a challenge [74], other aspects of high-quality comparative studies such as appropriate randomization, concealment of allocation from investigators, and blinded assessment of outcomes were not consistently conducted or reported. Effect sizes in RCTs are commonly overestimated if key methodological parameters such as these are not met [75]. These methodological issues necessitate the cautious interpretation of study results, and undermine the strength of conclusions that can be made regarding the effectiveness of HBOT.

Appraisal of the safety of HBOT was confounded by heterogeneity in the definition and reporting of adverse events. For example, some studies reported ear equalization problems as an adverse event, while others reported only patients requiring placement of myringotomy or tympanostomy tubes. A small number of studies stated that no "major" adverse events related to HBOT occurred without further definition, rendering these data unacceptable for the analysis of safety. The most commonly reported adverse events related to HBOT were barotraumas and visual changes. These were generally minor events that rarely led to discontinuation of HBOT and resolved shortly after cessation of therapy. Although claustrophobia or anxiety in the treatment chamber was reported in a small number of studies, treatment in multiplace hyperbaric chambers is becoming more commonplace and may reduce the incidence of such events. Oxygen toxicity of the central nervous system, a potentially more serious adverse event that manifests as seizures or convulsions, was reported in less than 1 % of patients. These seizures are believed to cause no residual effects [76], and rarely led to discontinuation of treatment. While an assessment of the safety of HBOT relative to other treatment regimens was not possible due to a lack of comparative evidence, absolute data indicates that HBOT is a safe and well-tolerated intervention for treatment of non-neurological STRI.

With respect to effectiveness, comparative evidence suggests that HBOT may provide clinical benefits as an adjunct to conventional treatment for particular non-neurological STRI over conventional treatment without HBOT. For radiation proctitis, RCT evidence indicated that patients with adjunctive HBOT had higher probability of healing and greater improvements in radiation-induced morbidity and quality of life, albeit over short periods of follow-up. RCT evidence also showed some clinical benefit for HBOT as an adjunct to conventional treatments in patients requiring surgery to irradiated soft tissue of the head and neck. However, these results should be considered with caution due to concerns regarding the methodological quality of the evidence base, and the circumscribed nature of the wounds treated (i.e., myocutaneous grafts and tooth socket wounds).

Favorable results for the effectiveness of HBOT were not found for all STRI. Evidence from a well-designed RCT examining the treatment of radiation-induced soft tissue lymphedema showed no significant improvements in clinical outcomes or quality of life after HBOT. This suggests that soft tissue lymphedema may possess a resistance to HBOT similar to that found in neurological tissue, and that treatment with HBOT may not be appropriate. Comparative evidence also failed to show a clinical benefit for HBOT for treatment of radiation cystitis, although this evidence was of low methodological quality and possibly impacted by patients receiving HBOT being considerably older than those included in other studies. These findings highlight the potential risk in assuming that all STRI respond to HBOT with comparable degrees of success.

While HBOT may offer clinical benefits as an adjunct to conventional therapy for particular STRI, the findings of two recently published comparative studies, including one RCT, provide results regarding its value relative to more definitive STRI treatments [34, 31]. These studies found equivalent clinical outcomes between HBOT and instillation of hyaluronic acid for radiation cystitis, and between HBOT and APC for radiation proctitis.

Given the current global constraints on health resources and growing concerns about the appropriate use of medical technologies, it is crucial for technologies to demonstrate both clinical- and cost-effectiveness in appropriate areas of application. This issue is especially pertinent to hyperbaric medicine due to HBOT commonly being employed as an adjunctive treatment, and health economics in this area having been noted to be deficient [77, 21]. It is crucial for appropriate cost-effectiveness evidence to be available for policy makers to make objective judgments regarding resource allocation, lest this may negatively impact on acceptance and funding of HBOT for specific indications or the field as a whole [78, 79]. One such example is an economic analysis based primarily on high-quality RCT evidence derived from the current review [28], which found HBOT to be a cost-effective alternative to usual care for the treatment of radiation proctitis [80, 24].

In summary, the findings of this evidence-based review indicate that HBOT may offer some clinical benefit to patients suffering from radiation proctitis and STRI of the head and neck. However, there remains a need to further validate the potential benefits of HBOT for individual types of non-neurological STRI, including the aforementioned conditions, both as an adjunct to conventional treatments and relative to definitive treatments. To ensure that relevant data is produced and potential benefits of HBOT for treatment of STRI are maximized, it is recommended that additional well-designed clinical trials be conducted via collaborative research efforts among institutions, practitioners, and researchers. These studies will be required to have appropriate statistical power to report outcomes of interest, longer-term follow-up to validate durability of response to HBOT, comprehensive reporting of adverse events to allow a determination of relative safety, and where possible should also include cost-effectiveness data and analysis. The HORTIS project, which included the RCT by Clarke and colleagues [28] as one of eight planned trials, appears to have been terminated due to low recruitment [81], highlighting one of the key challenges to be overcome. However, it is encouraging to note that a number of other clinical trials, including HOPON (prevention of osteoradionecrosis), RICH-ART (radiation cystitis), and HOT-II (STRI following radiotherapy for pelvic cancer), are in progress, with their results awaited with anticipation.

Acknowledgments Special thanks are due to Professor Guy Maddern for facilitating this research, Paula Cronin and Dr Stephen Goodall from the Center for Health Economics Research and Evaluation for their assistance in undertaking economic analyses, and the members of the MSAC advisory panel for their advice on clinical content during the course of the original systematic review.

Conflicts of interest The authors report no financial interests or other competing interests with respect to this publication. No manufacturer funded this research or played any role in conducting the study, collection of data, or presentation of results.

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