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Medical Policy Manual Medicine, Policy No. 14

Hyperbaric Oxygen Pressurization (HBOT)

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hyperbaric oxygen therapy (HBOT) is a technique of delivering higher pressures of oxygen to the tissues. Two methods of administration are available, systemic and topical.

MEDICAL POLICY CRITERIA

I. Topical hyperbaric and topical normobaric oxygen therapies are considered **investigational**.

II. Systemic hyperbaric oxygen therapy

A. Systemic hyperbaric oxygen therapy (HBOT) services must comply with the following guidelines which are consistent with the Undersea and Hyperbaric Medical Society criteria:

1. Patient must breathe 100% oxygen intermittently or continuously while the pressure of the treatment chamber is increased above one atmosphere absolute
2. Systemic hyperbaric oxygen pressurization should be at least 1.4 atmospheres absolute (atm abs) (20.5 psi)
3. Treatment is provided in a hospital or clinic setting.

B. Systemic hyperbaric oxygen pressurization (i.e., 100% oxygen delivered within a

chamber at a pressure of at least 1.4 atm abs) may be considered **medically necessary** in the treatment of any of the following conditions:

1. Acute carbon monoxide poisoning *(Recommended treatment review threshold*: 5 treatments)
2. Acute traumatic ischemia (*Recommended treatment review threshold:* Reperfusion injury – 1 treatment; Crush injury – 12 treatments (3 times per day for 2 days, then twice a day for 2 days, then daily for 2 days); Compartment syndrome – 3 treatments (twice a day for 1 day, then 1 treatment on day 2)
3. Chronic refractory osteomyelitis (*Recommended treatment review threshold*: 40 treatments)
4. Cyanide poisoning, acute (*Recommended treatment review threshold*: 5 treatments)
5. Decompression sickness (*Recommended treatment review threshold*: 10 treatments)
6. Gas or air embolism, acute (*Recommended treatment review threshold*: 10 treatments)
7. Gas gangrene (i.e., clostridial myositis and myonecrosis; **Recommended treatment review threshold*: 10 treatments)
8. Non-healing diabetic wounds of the lower extremities as an adjunct to ongoing conventional wound care in patients who meet **all** of the following 3 criteria (*Recommended treatment review threshold*: 30 treatments (one or two treatments daily):
    a. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes
    b. Patient has a wound classified as Wagner grade 3 or higher (see Policy Guidelines)
    c. Patient has no measurable signs of healing after 30 days of an adequate course of standard wound therapy including **all** of the following:
        i. Assessment of vascular status and correction of any vascular problems in the affected limb if possible
        ii. Optimal glycemic control
        iii. Optimal nutritional status
        iv. Topical wound treatment (eg, saline, hydrogels, hydrocolloids, alginates) with maintenance of a clean, moist bed of granulation tissue
        v. Debridement to remove devitalized tissue, any technique
        vi. Pressure reduction or offloading
        vii. Treatment to resolve infection (e.g., antibiotics)

9. Pre- and post-treatment for patients undergoing dental surgery (non-implant-related) of an irradiated jaw
10. Profound anemia with exceptional blood loss: only when blood transfusion is impossible or must be delayed (Recommended treatment review threshold: HBOT should be continued with taper of both time and frequency until red blood cells have been satisfactorily replaced by patient regeneration or the patient can undergo transfusion.)
11. Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis) and osteoradionecrosis *(*Recommended treatment review threshold for mandibular osteoradionecrosis: 60 treatments)
12. Idiopathic Sudden Sensorineural Hearing Loss of greater than or equal to 41 decibels and an onset of treatment within 14 days (*Recommended treatment review threshold:* 20 treatments.)
13. Necrotizing soft tissue infections
14. Actinomycosis
15. Central retinal artery occlusion

C. Hyperbaric oxygen pressurization is considered **investigational** for all other indications including but not limited to other ophthalmologic conditions, non-diabetic wounds, diabetic wounds with Wagner classification of grade 0-2, and acute thermal burns.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Indication for the requested service including type of HBOT planned
- Treatment plan including the following:
  - Percent of oxygen that the patient will breathe while receiving therapy
  - Pressurization (atm abs, psi)
  - Treatment setting
- Condition being treated including how many treatments being requested
  - If a diabetic wound is being treated then the request must include the following:
    - Type of diabetes
    - Location of wound
    - Wagner Classification
    - Measurable signs of healing following standard wound therapy including therapy length of time with documentation of the following:
      - Vascular assessment and correction, if possible, of vascular problems to affected area
      - Glycemic data for patient (e.g., A1C)
      - Nutritional status

        - Topical wound treatments utilized including wound bed description
        - Debridement
        - Pressure reduction or offloading
        - Any infection treatment utilized
    - If dental surgery, include description and diagnosis
    - If anemia, include blood loss and ability to transfuse patient
    - If necrosis, include type
    - If idiopathic sudden sensorineural hearing loss, include decibels of loss and onset of treatment

WAGNER CLASSIFICATION

- Grade 0: No open lesion
- Grade 1: Superficial ulcer without penetration to deeper layers
- Grade 2: Ulcer penetrates to tendon, bone, or joint
- Grade 3: Lesion has penetrated deeper than grade 2 and there is abscess, osteomyelitis, pyarthrosis, plantar space abscess, or infection of the tendon and tendon sheaths
- Grade 4: Wet or dry gangrene in the toes or forefoot
- Grade 5: Gangrene involves the whole foot or such a percentage that no local procedures are possible and amputation (at least at the below the knee level) is indicated

CROSS REFERENCES

None

BACKGROUND

SYSTEMIC HBOT

In systemic or large chamber hyperbaric oxygen, the patient is entirely enclosed in a pressure chamber and breathes oxygen at a pressure greater than 1 atmosphere (atm, the pressure of oxygen at sea level). Thus, this technique relies on systemic circulation to deliver highly oxygenated blood to the target site, typically a wound. In addition, systemic hyperbaric oxygen therapy can be used to treat systemic illness, such as air or gas embolism, carbon monoxide poisoning, clostridial gas gangrene, etc. Treatment may be carried out either in a monoplace chamber pressurized with pure oxygen or in a larger, multiplace chamber pressurized with compressed air, in which case the patient receives pure oxygen by mask, head tent, or endotracheal tube.

Mild Hyperbaric Oxygen Therapy

Oxygen therapy delivered via soft-sided chambers is referred to as mild hyperbaric oxygen therapy. While this implies that these chambers provide HBOT, the therapy is not considered hyperbaric as they provide pressurization of only about 4.5 psi, compared with true HBOT which is defined as pressurization of 20.5 psi or higher.

TOPICAL OXYGEN THERAPY

Topical Hyperbaric Oxygen Therapy

Topical hyperbaric oxygen therapy is a technique of delivering 100% oxygen directly to an open, moist wound at a pressure slightly higher than atmospheric pressure. It is hypothesized that the high concentrations of oxygen diffuse directly into the wound to increase the local cellular oxygen tension, which in turn promotes wound healing. This therapy has been investigated as a treatment of skin ulcerations resulting from diabetes, venous stasis, postsurgical infection, gangrenous lesion, decubitus ulcers, amputations, skin graft, burns, or frostbite.

Topical hyperbaric oxygen devices consist of an appliance to enclose the wound area (frequently an extremity) and a source of oxygen; conventional oxygen tanks may be used. Topical hyperbaric oxygen therapy may be performed in the office, clinic, or may be self-administered by well-trained patients in the home. Typically, the therapy is offered for 90 minutes per day for 4 consecutive days. After a 3-day break, the cycle may be repeated. The regimen may last for 8 to 10 weeks.

Topical Normobaric Oxygen Therapy

Devices that deliver topical oxygen to a wound at normal atmospheric pressure (normobaric) are not considered hyperbaric oxygen therapy. These devices may also be called low dose tissue oxygenation systems. An example of a normobaric oxygen delivery system is the TransCu O2™, a small handheld device with an attached cannula. According to the manufacturer, the TransCu O2 is “intended for use with wound dressings to treat the following: skin ulcerations due to diabetes, venous stasis, post-surgical infections and gangrenous lesions; pressure ulcers; infected residual limbs; skin grafts; burns; and frostbite.” The device concentrates room air to 99.9% oxygen which is delivered via the cannula which is placed under the wound dressing.

REGULATORY STATUS

In 2013, U.S. Food and Drug Administration (FDA) published a statement warning that non-FDA approved uses of HBOT may endanger the health of patients.[1] “Patients may incorrectly believe that these devices have been proven safe and effective for uses not cleared by FDA, which may cause them to delay or forgo proven medical therapies. In doing so, they may experience a lack of improvement and/or worsening of their existing condition(s).”

The following are examples of oxygen therapy devices:

In February 1999, the Numobag™ Kit (Numotech, Inc) for application of topical hyperbaric therapy was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices. Another example is the AOTI Hyper-Box™ (AOTI Ltd., Galway, Ireland) which was cleared by FDA in 2008.

In August 2009, the TransCu O2 (Electrochemical Oxygen Concepts, Inc.) was cleared for marketing by the FDA through the 510(k) process as substantially equivalent to existing devices.

There are numerous FDA-approved hyperbaric oxygen chambers. In May 2005, the ATA Monoplace Hyperbaric System (ATA Hyperbaric Chamber Manufacturing, Inc.) was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing hyperbaric devices.

EVIDENCE SUMMARY

Current evidence is sufficient to determine the effectiveness of hyperbaric oxygen therapy (HBOT) for the indications that meet the above medical necessity criteria. Assessing the effectiveness and safety of HBOT for the investigational indications requires randomized controlled trials comparing HBOT with the conventional treatments for each indication. Therefore, the following literature review on HBOT focuses on randomized controlled trials (RCTs) and systematic reviews of RCTs for the investigational indications.

Assessment of efficacy for therapeutic interventions involves a determination of whether the intervention improves health outcomes. The optimal study design for a therapeutic intervention is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. When the primary outcomes are subjective (e.g., pain, depression), sham-controlled RCTs are needed to assess the effect of the intervention beyond that of a placebo effect.

TOPICAL HYPERBARIC OXYGEN

Due to their different methods of delivery, topical and systemic hyperbaric oxygen are distinct technologies such that they must be examined separately.[2] There is minimal published literature regarding topical hyperbaric oxygen therapy. A 2015 Cochrane review of interventions for treating gas gangrene evaluated the safety and efficacy topical HBOT and Chinese herbs as treatments options.[3] Re-analysis if cure rate did not show beneficial effects from either treatment. In 1984, Heng and colleagues published a controlled study of topical hyperbaric oxygen therapy in 6 patients with 27 ulcers compared to no treatment in 5 patients with 10 ulcers.[4] Although a greater improvement was noted in the treated group, the results were calculated according to the number of ulcers rather than based on individual patients. Leslie and colleagues reported on a trial that randomly assigned 18 patients with diabetic foot ulcers to receive either topical hyperbaric oxygen therapy plus standard wound care or standard wound care alone.[5] Changes in ulcer size and depth did not differ between the 2 groups. Other studies consist of anecdotal reports or uncontrolled case series.[6]

SYSTEMIC HYPERBARIC OXYGEN THERAPY (HBOT)

In-home Hyperbaric Oxygen

A position statement from the National Board of Diving & Hyperbaric Medical Technology on in-home HBOT has been published on the Web site for The Undersea and Hyperbaric Medicine Society (UHMS).[7] The statement indicates that in-home HBOT “is inherently unsafe and cannot be condoned.” This position is based on concern for the safety and well-being of patients as well as those people in proximity to the HBOT delivery system because in-home provision of HBOT is likely to:

- Bypass otherwise mandatory federal, state, and local codes related to design, construction, installation, and operation of these devices; and
- Occur without adequate physician oversight and the operational support of appropriately qualified HBOT providers.

Acute Coronary Syndromes

Systematic Reviews

A 2012 Cochrane review by Bennett and colleagues identified 6 trials with a total of 665 patients evaluating HBO for acute coronary syndrome.[8] All of the studies included patients with acute myocardial infarction (MI); one study also included individuals presenting with unstable angina. Additionally, all trials used HBOT as an adjunct to standard care. Control interventions varied; only 1 trial described using a sham therapy to blind participants to treatment group allocation. In a pooled analysis of data from 5 trials, there was a significantly lower rate of death in patients who received HBOT compared to a control intervention (RR: 0.58: 0.36 to 0.92). Due to variability of outcome reporting in the studies, few other pooled analyses could be conducted. A pooled analysis of data from 3 trials on improvements in left ventricular function did not find a statistically significant benefit of HBOT (RR: 0.09; 95% CI: 0.01 to 1.4). The authors noted that, although there is some evidence from small trials that HBOT is associated with a lower risk of death, larger trials with high methodologic quality are needed in order to determine which patients, if any, can be expected to derive benefit from HBOT. Therefore, HBOT is considered investigational in the treatment of acute coronary syndromes.

Autism Spectrum Disorders (ASD)

Systematic Reviews

A 2016 systematic review on hyperbaric oxygen therapy for treatment of children with autism identified one RCT[9] with a total of 60 children. The study quality was rated as low using GRADE criteria with small sample size and wide confidence intervals. The results indicated no improvement in social interaction and communication, behavioral problems, communication and linguistic abilities, or cognitive function. The authors reported minor-grade ear barotrauma as adverse events.

A 2012 systematic review[10] of RCTs on hyperbaric oxygen therapy for treatment of children with autism identified two RCTs[11,12]with a total of 89 participants. In both RCTs the active hyperbaric treatment was 24% oxygen delivered at an atmospheric pressure of 1.3 atmospheres (atm). Although this regimen was referred to as HBOT in the article, it differed from standard HBOT which uses 100% oxygen and a pressure of at least 1.4 atm. A detailed analysis of these RCTs is provided below. Briefly, one of the two RCTs found better outcomes after hyperbaric oxygen compared with placebo treatment, and the other did not find significant differences in outcomes. The author concluded that additional sham-controlled trials with rigorous methodology are needed in order to draw conclusions about the efficacy of HBOT for treating autism.

Randomized Controlled Trials (RCTs)

The following is a summary of the 2 RCTs reported in the above systematic review:

- One of the above two RCTs was by Rossignol and colleagues.[11] This study was a double-blind RCT that included 62 children, ages 2-7, meeting DSM-IV criteria for autistic disorder. The active treatment was hyperbaric treatment at 1.3 atmospheres (atm) and 24% oxygen in a hyperbaric chamber. (This regimen differs from standard HBOT which uses 100% oxygen and a pressure of at least 1.4 atm). The other group received a sham treatment consisting of 1.03 atm and ambient air (21% oxygen). Both groups received 40 sessions of active or sham treatment lasting 60 minutes each over a

period of 4 weeks. The equipment, procedures, etc. in the two groups were as similar as possible to maintain blinding. The investigators, participants, parents, and clinic staff were blinded to treatment group. Only the hyperbaric technician, who had no role in outcome assessment, was aware of group assignment. After completion of the 4-week study, families with children in the control group were offered the active intervention. When asked at the end of the study, there was no significant difference in the ability of parents to correctly guess the group assignment of their child.

The outcomes were change compared to baseline after 4 weeks on the following scales: Aberrant Behavior Checklist (ABC) total score and 5 subscales; Autism Treatment Evaluation Checklist (ATEC) total score and 4 subscales; and Clinical Global Impression-Improvement (CGI) overall functioning score and 18 subscales. P values of <0.05 were considered statistically significant; there was no adjustment for multiple comparisons. The analysis included all children who completed at least one complete session. Of the 33 children assigned to active treatment, 30 were included in the analysis and 29 completed all 40 treatments. Of the 29 children assigned to the control treatment, 26 completed all 40 sessions and were included in the analysis.

There was no significant between-group improvement on the ABC total score, any of the ABC subscales, or on the ATEC total score. Compared to the control group, the treatment group had a significant improvement in 1 of 4 subscales of the ATEC, the sensory/cognitive awareness subscale. The change from baseline on this subscale was a mean of 16.5 in the treatment group and a mean of 5.4 in the control group, a difference of 11.1 (p=0.037). (Note: due to an administrative error, baseline ATEC was not collected at one site, and thus data were not available for 23 children in the treatment group and 21 children in the control group). On the physician-rated CGI total score, 9/30 (30%) children in the treatment group had a score of 1 (very much improved) or 2 (much improved) compared to 2/26 (8%) in the control group (p=0.047). On the parental-rated CGI total score, 9/30 (30%) children in the treatment group had a score of 1 or 2 compared to 4/26 (15%) in the control group (p=0.22, not statistically significant). (The exact numbers receiving scores of 1 vs. 2 were not reported). Change in mean CGI scores were also reported, but this may be a less appropriate way to analyze these data. Among the parental-rated CGI subscales, significantly more children were rated as improved in the treatment group compared to control on 2 out of 18 subscales, receptive language (p=0.017) and eye contact (p=0.032).

A key limitation of this study was that the authors reported only outcomes at 4 weeks, directly after completion of the intervention. It is not known whether there are any long-term effects. Additional follow-up data cannot be obtained because members of the control group crossed over to the intervention after 4 weeks. Other limitations included lack of adjustment for multiple comparisons and unclear clinical significance of the statistically significant outcomes. The Undersea and Hyperbaric Medical Society (UHMS) issued a position paper after publication of the Rossignol et al. study stating that they still did not recommend routine treatment of autism with HBOT.[13]

- The other RCT included in the systematic review was a double-blind RCT that began with 46 children with autism, ages 2-14 years, who were matched in pairs according to age and the number of hours of Applied Behavior Analysis (ABA) treatment they were receiving at the start of the study. Randomized[12] treatment allocation of the matched

pairs was by coin toss. Both groups received 80 1-hour sessions of active treatment (24% oxygen at 1.3 atm) or sham treatment (room air at ambient pressure) for up to 15 weeks. Participants were allowed to undergo ABA, take any supplements, pharmacological interventions, and dietary modifications. Twelve patients withdrew from the trial, leaving 18 patients in the treatment group and 16 in the control group.

The primary outcome of change in symptoms was based on direct observation and the scales noted in the Rossignol et al. study above in addition to the Behavior Rating Inventory of Executive Functioning (BRIEF), Parent Stress Index (PSI), Peabody Picture Vocabulary Test (PPVT-III), Repetitive Behavior Scale (RBS), and the Vineland Adaptive Behavior Scales (VABS-II). Direct observation and intention to treat analysis of test scores found no significant difference on any outcome measures between the treatment and sham groups. No participants experienced adverse effects attributable to barotrauma (e.g., pressure injury to tympanic membranes or sinuses).

A limitation of this study was the small sample size which was determined to be adequate to detect only large effects, which were not present in this study. In addition, since some patients in both groups received intensive ABA interventions during the study period, any potential effects of HBOT could not be isolated. The authors concluded that the active treatment had no significant beneficial effect on ASD and was not recommended for the treatment of ASD symptoms.

One additional RCT not included in the systematic review above was identified:

A 2012 RCT published after the systematic review randomly assigned 60 children with autism to receive 20 one-hour sessions with HBOT or sham air treatment (n=30 per group).[14] The primary outcome measures were change in the ATEC and CGI, evaluated separately by clinicians and parents. There were no statistically significant differences between groups on any of the primary outcomes. For example, post-treatment clinician-assessed mean scores on the ATEC were 52.4 in the HBOT group and 52.9 in the sham air group.

Conclusion

There is insufficient evidence from well-designed RCTs that HBOT improves health outcomes for patients with autism spectrum disorder; therefore, HBOT therapy for this indication is considered investigational.

Bell's Palsy

Systematic Review

In 2012, Holland and colleagues published a Cochrane review evaluating HBOT in adults with Bell's palsy.[15] The authors identified one RCT with 79 participants, and this study did not meet the Cochrane review methodologic standards because the outcome assessor was not blinded to treatment allocation. Therefore, the evidence is insufficient to permit conclusions and HBOT is considered investigational for the treatment of Bell's palsy.

Randomized Controlled Trials (RCTs)

No RCTs have been published since the 2012 Cochrane review.

Bisphosphonate-related Osteonecrosis of the Jaw (BRONJ)

Randomized Controlled Trials (RCTs)

An unblinded RCT was published by Freiberger and colleagues in 2012 on use of HBOT as an adjunct therapy for patients with bisphosphonate-related osteonecrosis of the jaw.[16] Forty-nine patients were randomly assigned to HBOT in addition to standard care (n=22) or standard care alone (n=27). Five patients in the standard care group received HBOT and 1 patient assigned to the HBOT group declined HBOT. The investigators decided to do a *per* protocol (PP) analysis (actual treatment received) because of the relatively large degree of crossover. Participants were evaluated at 3, 6 12 and 18 months. Data were available on 46 patients, 25 received HBOT in addition to standard care and 21 received standard care alone. The primary outcome measure was change in oral lesion size or number. When change from baseline to last available follow-up was examined, 17 of 25 (68%) of HBO-treated patients had improvement in oral lesion size or number compared to 8 of 21 (38%) in the standard care group, p=0.043. When change from baseline to 6, 12 or 18 months was examined, there was not a statistically significant difference between groups in the proportion of patients with improvement. In addition, the proportion of patients who healed completely did not differ significantly between groups at any time point. This single trial does not report consistent findings of benefit across outcome measures. It also has a number of methodologic limitations, e.g., unblinded, cross-over, and analysis performed on a *per-protocol* basis rather than intention to treat. A disadvantage of the *per-protocol* analysis is that randomization is not preserved, and the two groups may differ on characteristics that affect outcomes. As a result, this trial is insufficient to conclude that HBOT improves health outcomes for patients with bisphosphonate-related osteonecrosis of the jaw.

Conclusion

Current evidence is insufficient to determine the safety and efficacy of HBOT in the treatment of bisphosphonate-related osteonecrosis of the jaw. Therefore, HBOT is considered investigational for this indication.

Cancer Treatment

Randomized Controlled Trials (RCTs)

In an RCTof 32 patients, Heys and colleagues found no increase in 5-year survival in patients treated with HBOT prior to chemotherapy for locally advanced breast carcinoma to increase tumor vascularity.[17] This approach is being studied since studies in animal models have suggested that HBOT increases tumor vascularity and thus may make chemotherapy more effective. In a Cochrane review, Bennett and colleagues concluded that HBOT given with radiotherapy may be useful in tumor control; however, the authors expressed caution since significant adverse effects were common with HBOT and indicated further study would be useful.[18]

Conclusion

Current evidence is insufficient to determine the safety and efficacy of HBOT in the treatment of cancer of any type and location. Therefore, HBOT is considered investigational for this indication.

Cerebral Palsy

Randomized Controlled Trials (RCTs)

- In 2012, Lacey and colleagues published a double-blind RCT that included 49 children age 3-8 years with spastic cerebral palsy.[19] Participants were randomized to receive 40 treatments with either HBOT (n=25) or hyperbaric air to simulate 21% oxygen at room air (n=24). The primary efficacy outcome was change in the Gross Motor Function Measure (GMFM-88) global score after the 8-week treatment period. The study was stopped early due to futility, when an interim analysis indicated that there was less than a 2% likelihood that a statistically significant difference between groups would be found. At the time of the interim analysis, there was no significant between-group difference in the post-treatment GMFM-88 global score (p=0.54).

- In the largest RCT to date, Collet et al. randomly assigned 111 children with cerebral palsy to 40 treatments over a 2-month period of either HBOT (n=57) or slightly pressurized room air (n=54).[20] The authors found HBOT and slightly pressurized air produced similar improvements in both groups for outcomes such as gross motor function and activities of daily living.

Conclusion

HBOT is considered investigational as a treatment for cerebral palsy because it has not been shown to provide additional health benefits in this patient population.

Compromised Skin Grafts and Flaps

Systematic Reviews

- In a 2010 Cochrane review, Estes and colleagues found a lack of high quality evidence regarding HBOT in the treatment of skin grafts and flaps.[21,22] The authors found one randomized controlled trial (RCT) on skin grafts for burn wounds (n=48) which reported significantly higher graft survival with HBOT, and one RCT on flap grafting (n=135) which reported no significant differences in graft survival with HBOT compared with dexamethasone or heparin. However, these data are unreliable due to various methodologic limitations such as biased analysis, omitted data, and small size.

- In 2006, Friedman and colleagues published a systematic review of literature on use of HBOT for treating skin flaps and grafts.[23] No RCTs were found. The authors identified 2 retrospective case series on use of HBOT for clinically compromised skin grafts and flaps. The series had sample sizes of 65 and 26, respectively; both were published in the 1980s based on treatment provided in the 1970s and 1980s.

Randomized Controlled Trials (RCTs)

No RCTs have been published since the above systematic reviews.

Conclusion

Although the study of HBOT for compromised skin grafts and flaps goes back several decades, the clinical trial data is limited to noncomparative case series and a single randomized controlled trial. This evidence is insufficient to determine the safety and efficacy of HBOT in the treatment of compromised skin grafts and flaps. Therefore, HBOT is considered investigational for these indications.

Carbon Monoxide Poisoning

A 2011 Cochrane review of 7 RCTs concluded that the available evidence is insufficient to determine whether adverse neurologic outcomes in patients with carbon monoxide poisoning are reduced with HBOT.[24] In 2008, the American College of Emergency Physicians (ACEP) published a clinical policy on critical issues in carbon monoxide poisoning.[25] Their literature review indicated there was only level C evidence (preliminary, inconclusive, or conflicting evidence) for treatment of acute carbon monoxide poisoning. The 2008 UHMS guidelines, however, list carbon monoxide poisoning as an indication for HBOT.

Two blinded randomized trials were discussed in both the Cochrane and ACEP reviews. One is a study by Scheinkestel et al, a double-blind, RCT comparing HBOT with normobaric oxygen in patients with carbon monoxide poisoning.[26] The authors reported that HBOT did not benefit patient outcomes of neuropsychologic performance when HBOT was completed and at 1-month follow-up. This study was limited, however, by a high rate (46%) of patients who were lost to follow-up. Moreover, the trial has been criticized for administrating 100% normobaric oxygen for at least 72 hours between treatments, which has been called a toxic dose of oxygen.[27] The critiques also mention that there was an unusually high rate of neurologic sequelae after the treatment period, which could be due in part to the high dose of oxygen and/or the high rate of cognitive dysfunction in the study population (69% were poisoned by carbon monoxide through suicide attempts).

The other blinded trial, by Weaver et al, also compared hyperbaric and normobaric oxygen.[28] Patients received either 3 sessions of HBOT or 1 session of normobaric oxygen plus 2 sessions of exposure to normobaric room air. The primary outcome was the rate of cognitive sequelae at 6 weeks. Cognitive function was assessed using a battery of neuropsychological tests. At the 6-week follow-up, the intention- to-treat analysis found that 19 of 76 (25.0%) in the HBOT group and 35 of 76 (46.1%) in the control group had cognitive sequelae; the difference was statistically significant (p=0.007). There was a high rate of follow-up at 6 weeks, 147 of 152 (97%) of randomized patients. Enrollment in the study was stopped early because an interim analysis found HBOT to be effective. A follow-up study, which included 147 patients from the randomized trial and 75 who had been eligible for the trial but had not enrolled, was published in 2007.[29] Of the group treated with HBOT (n=75), cognitive sequelae were identified in 10 of 58 (17%) at 6 months and 9 of 62 (14%) at 12 months. Of the group not treated with HBOT (n=163), 44 of 146 (30%) at 6 months and 27 of 149 (18%) at 12 months had cognitive sequelae. (The follow-up rate was higher at 12 months because the investigators received additional funding for data collection.)

Delayed-Onset Muscle Soreness

Systematic Review

In a 2005 Cochrane review, Bennett and colleagues concluded that available evidence is insufficient to demonstrate beneficial outcomes with HBOT for delayed-onset muscle soreness and closed soft-tissue injury.[30] It was noted that HBOT possibly even increases pain initially and further studies are needed. Therefore, use of HBOT for this indication is considered investigational.

Randomized Controlled Trials (RCTs)

No RCTs have been published since the 2005 Cochrane review.

Dementia

Systematic Review

A 2012 Cochrane review identified 1 RCT evaluating HBOT for the treatment of vascular dementia.[31] The 2009 study compared HBOT plus donepezil to donepezil-only in 64 patients. The HBOT and donepezil group had significantly better cognitive function after 12 weeks of treatment, as assessed by the Mini-Mental State Examination. However, the Cochrane investigators judged the trial to be of poor methodologic quality because it was not blinded and the methods of randomization and allocation concealment were not discussed.

Randomized Controlled Trials (RCTs)

No RCTs have been published since the 2012 Cochrane review.

Conclusion

The current evidence for HBOT as a treatment of dementias of any cause is limited to a single short-term clinical trial on vascular dementia. This evidence is insufficient to permit conclusions about the safety and efficacy of HBOT on vascular dementia. No other randomized controlled trials were found for HBOT as a treatment of demential from any cause. Due to the lack of sufficient evidence, HBOT is considered investigational for treatment of dementias.

Femoral Neck Necrosis, Idiopathic

Randomized Controlled Trials (RCTs)

In 2010, Camporesi and colleagues published the results of a double-blind RCT that evaluated HBOT in 20 adult patients with idiopathic unilateral femoral head necrosis.[32] Patients received 30 treatments over 6 weeks with either HBOT at 2.5 ATA (n=10) or a sham treatment consisting of hyperbaric air (n=10). The mean severity of pain on a 0-to-10 scale was significantly lower in the HBOT group than the control group after 30 sessions ($p<0.001$) but not after 10 or 20 sessions. (The article did not report exact pain scores). Several range-of-motion outcomes were also reported. At the end of the initial treatment period, extension, abduction and adduction, but not flexion, were significantly greater in the HBOT group compared to the control group. Longer-term comparative data were not available because the control group was offered HBOT at the end of the initial 6-week treatment period.

Conclusion

The current evidence is limited to a single, small short-term RCT. Thus, there is insufficient data on which to draw conclusions about the efficacy of HBOT for treating femoral head necrosis, and it is considered investigational for this indication.

Fibromyalgia

One quasi-randomized trial and 1 delayed-treatment RCT on HBOT for fibromyalgia were identified. In 2004, a study by Yildiz et al included 50 patients with fibromyalgia who had ongoing symptoms despite medical and physical therapy.[33] On an alternating basis, patients were assigned to HBOT or a control group. The HBOT consisted of fifteen 90-minute sessions at 2.4 ata (1 session per day, 5 d/wk). The control group breathed room air at 1 ata on the same schedule. Baseline values on the 3 outcomes were similar in the 2 groups. After the

course of HBOT treatment, the mean (SD) number of tender points were 6.04 (1.18) in the HBO group and 12.54 (1.10) in the control group. The mean (SD) pain threshold was 1.33 kg (0.12) and 0.84 kg (0.12), respectively, and the mean VAS was 31.54 (8.34) and 55.42 (6.58), respectively. In the study abstract, the authors stated that there were statistically significant differences between the HBO and control groups after 15 therapy sessions, but the table presenting outcomes lacked the notation used to indicate between-group statistical significance. It is not clear whether the control group actually received a sham intervention that would minimize any placebo effect ie whether or not the control intervention was delivered in a hyperbaric chamber. The authors stated that the study was double-blind but did not specify any details of patient blinding.

In 2015, Efrati et al published an RCT that included 60 female patients who had fibromyalgia for at least 2 years and were symptomatic.[34] Patients were randomized to an immediate 2 month course of HBOT or delayed HBOT after 2 months. The HBOT protocol was forty 90-minute sessions of 100% oxygen at 2 ata (1 session per day, 5 d/wk). Forty-eight of 60 patients (80%) completed the study and were included in the analysis. After the initial 2 months, outcomes including number of tender points, pain threshold, and quality of life (SF-36) were significantly better in the immediate treatment group compared with the delayed treatment group (which received no specific intervention during this time). After the delayed treatment group had undergone HBOT, outcomes were significantly improved compared with scores prior to HBOT treatment. These findings are consistent with a clinical benefit of HBOT, but also with a placebo effect. A sham-control is needed to confirm the efficacy of HBOT in the treatment of fibromyalgia and other conditions where primary end points are pain and other subjective outcomes.

The above studies were few in number with relatively small sample sizes and had methodological limitations, e.g., quasi-randomization and no or uncertain sham control for a condition with subjective outcomes susceptible to a placebo effect. Moreover, the HBO protocol varied (e.g., 15 HBOT sessions vs 40 HBOT sessions). Thus, the evidence is insufficient to draw conclusions about the impact of HBOT on health outcomes for patients with fibromyalgia.

Fracture Healing

Systematic Review

In 2012, Bennett and colleagues published a Cochrane review on HBOT to promote fracture healing and treat non-union fractures.[35] The investigators did not identify any published RCTs on this topic that compared HBOT to no treatment, sham treatment, or another intervention and reported bony union as an outcome.

Randomized Controlled Trials (RCTs)

No RCTs have been published since the 2012 Cochrane review.

Conclusion

Due to the lack of RCTs, it is not possible to conclude whether the use HBOT to promote fracture healing improves outcomes; therefore, the use of HBOT for this indication is considered investigational.

Headaches

When assessing any treatment focused on pain relief, randomized, placebo-controlled trials are necessary to investigate the extent of any placebo effect and to determine whether any improvement with the treatment exceeds that associated with a placebo.

The following is a summary of the available evidence:

Migraine headaches

- Systematic Review

  A 2008 Cochrane review by Bennett and colleagues identified RCTs that evaluated the effectiveness of systemic hyperbaric oxygen therapy for preventing or treating migraine headache compared to another treatment or a sham control.[36] Five trials with a total of 103 patients were identified that addressed treatment of acute migraine with HBOT. A pooled analysis of 3 trials (total of 43 patients) found a statistically significant increase in the proportion of patients with substantial relief of migraine within 45 minutes of HBOT (relative risk [RR] 5.97, 95% confidence interval [CI]1.46-24.38, p=0.001). No other pooled analyses were conducted due to variability in the outcomes reported in the trials. The meta-analysis did not report data on treatment effectiveness beyond the immediate post-treatment period, and the methodologic quality of trials was moderate to low, e.g., randomization was not well-described in any trial. There was no evidence that HBOT could prevent episodes of migraine headache.

- Randomized Controlled Trials (RCTs)

  In 2004 Eftedal and colleagues reported the results of a randomized, double-blind, placebo-controlled trial to assess whether HBOT had a prophylactic effect on migraine headache. [37] Forty patients were randomly assigned to either a treatment group receiving 3 sessions of HBOT or a control group receiving 3 hyperbaric treatments with room air. Thirty-four patients completed the study. Efficacy was measured as the difference between pre- and post-treatment hours of headache per week. There was no significant reduction in hours of headache with HBOT compared with hyperbaric air treatments. Nor was there a significant difference in either group in pre- and post-treatment levels of endothelin-1 in venous blood. The authors concluded that that HBOT had no significant prophylactic effect on migraine headache or on the endothelin-1 level in venous blood.

Cluster headaches

- Systematic Reviews

  Two 2008 systematic reviews, including the Cochrane review noted above, reported few studies comparing HBOT with sham treatment for cluster headaches.[36,38] Available randomized, placebo-controlled trials measuring effect on symptoms are unreliable due to very small size.[39,40]

- Randomized Controlled Trials (RCTs)

  No RCTs have been published since the 2008 systematic reviews.

- Conclusion

  Due to the lack of sufficient evidence from well-designed clinical trial, HBOT for the treatment of headaches from any cause is considered investigational.

Herpes Zoster

Randomized Controlled Trial (RCT)

In 2012, Peng and colleagues published an RCT evaluating HBOT as a treatment of herpes zoster.[41] Sixty-eight patients with herpes zoster diagnosed within the previous 2 weeks were randomized to 30 sessions of HBOT (n=36) or medication treatment (n=32). Pharmacotherapy included antiviral, pain, nerve nutritive and antidepressive medication. Therapeutic efficacy was calculated at the end of the 3-week treatment period and included the proportion of patients who were healed (i.e., complete subsidence of pain and rash) or improved (i.e., significant pain relief and rash subsistence). Rates of therapeutic efficacy were 97.2% in the HBOT group and 81.3% in the medication group ($p<0.05$). Limitations of the study included a lack of blinding and lack of long-term follow-up.

Conclusion

The evidence from the single randomized controlled trial is insufficient to permit conclusions about the effect of HBOT on health outcomes for patients with herpes zoster; therefore, HBOT is considered investigational for this indication.

Inflammatory Bowel Disease

Systematic Reviews

A 2014 systematic review by Dulai et al examined the evidence on HBOT for inflammatory bowel disease (Crohn disease and ulcerative colitis).[42] The review was not limited by study design. The authors included 17 studies: 1 RCT, 2 case-control studies, 3 case series, and 11 case reports. The studies reported on a total of 613 patients, 286 with Crohn disease and 327 with ulcerative colitis. The only RCT identified was published in 2013; it was open-label and included 18 patients with ulcerative colitis.[43] Patients were randomized to treatment with standard medical therapy only (n=8) or medical therapy plus HBOT (n=10) consisting of 90-minute treatments at 2.4 atm, 5 days a week for 6 weeks (total of 30 sessions). The primary outcome was the self-reported Mayo score which has a potential range of 0 to 12.[44] Patients with a score of 6 or more are considered to have moderate to severe active disease. At 6 months follow-up there was no significant difference between groups in the Mayo score, with a median score of 0.5 in the HBOT group and 3 in the control group (exact p value not reported). In addition, there were no significant differences in any of the secondary outcomes including laboratory tests and fecal weight. Overall, the authors found that the studies had a high risk of bias, particularly in the areas of attrition and reporting bias, and further study in well-controlled, blinded RCTs was recommended.

Randomized Controlled Trials (RCTs)

No RCTs have been published since the 2014 systematic review.

Conclusion

There is insufficient evidence that HBOT is effective for treating inflammatory bowel disease. Only 1 small RCT has been published, and this study did not find a significant improvement in health outcomes when HBOT was added to standard medical therapy.

In Vitro Fertilization

In a 2005 nonrandomized pilot study, Van Voorhis and colleagues reported that HBOT was well tolerated in women undergoing ovarian follicular stimulation for in vitro fertilization; however no outcomes were reported.[45] Therefore, current evidence is insufficient to permit conclusions and HBOT is considered investigational for this indication.Mental Illness

A Rapid Response Report from the Canadian Agency for Drugs and Technologies in Health (CADTH) searched the literature through July 2014 on the clinical effectiveness of hyperbaric oxygen therapy for treatment of adults with posttraumatic stress disorder, generalized anxiety disorder, and/or depression.[46]

The review's inclusion criteria were health technology assessments, systematic reviews, meta-analyses, RCTs or nonrandomized studies comparing HBOT to any active treatment and reporting clinical outcomes. No eligible studies were identified.

Multiple Sclerosis

A Cochrane review of RCTs on HBOT for multiple sclerosis was published by Bennett et al in 2004.[47] The authors identified 9 RCTs, with a total of 504 participants that compared the effects of HBOT with placebo or no treatment. The primary outcome of the review was score on the Expanded Disability Status Scale (EDSS). A pooled analysis of data from 5 trials (N=271) did not find a significant difference in change in the mean EDSS after 20 HBOT treatments versus control (mean difference [MD], -0.07; 95% CI, -0.23 to 0.09). Moreover, a pooled analysis of data from 3 trials (n=163) comparing HBOT and placebo did not find a significant difference in mean EDSS after 6 months of follow-up (MD = -0.22; 95% CI, -0.54 to 0.09).

Osteomyelitis

No prospective clinical trials on chronic refractory osteomyelitis or acute refractory osteomyelitis were identified in updated searches. The justification for the use of HBOT in chronic osteomyelitis has been primarily based on case series. Among the larger case series, Maynor et al reviewed the records of all patients with chronic osteomyelitis of the tibia seen at one institution.[48] Follow-up data were available on 34 patients who had received a mean of 35 adjunctive HBO treatments (range, 6-99). Of the 26 patients with at least 2 years of follow-up after treatment, 21 (81%) remained drainage-free. Twelve of 15 (80%) with follow-up data at 60 months had remained drainage-free. A study by Davis et al reviewed outcomes for 38 patients with chronic refractory osteomyelitis treated at another U.S. institution.[49] Patients received HBOT until the bone was fully recovered with healthy vascular tissue; this resulted in a mean of 48 daily treatments (range, 8-103). After a mean posttreatment follow-up of 34 months, 34 of 38 (89%) patients remained clinically free of infection (i.e., drainage-free and no tenderness, pain, or cellulitis). Success rates from several smaller case series, all conducted in Taiwan, are 12 of 13 (92%) patients, 11 of 14 (79%) patients, and 13 of 15 (86%) patients.[50-52] A high percentage of refractory patients in these series had successful outcomes.

Radiotherapy Adverse Effects

Systematic Review

- A 2017 systematic review on the effectiveness of HBOT for the treatment of radiation-induced skin necrosis included eight articles with five case series studies, two case reports, and one observational cohort.[53] The authors investigated the change in symptoms and alteration in wound healing and reported that HBOT was a safe intervention with promising outcomes. However, the authors recommended additional high quality evidence in order for HBOT to be considered as a relevant treatment for this indication. s

- A 2014 systematic review on the safety and effectiveness of HBOT for the treatment of non-neurological soft tissue radiation-related injuries (STRI) included 41 articles, 11 of which compared regimens with and without HBOT.[54] Serious adverse effects were rare and the more common adverse effects were minor and self-limiting. Evidence of a beneficial effect of HBOT was reported radiation proctitis and STRI of the head and neck, but not for post-radiation soft tissue edema or radiation cystitis. The authors recommended further studies to validate the use of HBOT as both a definitive and adjunctive treatment for individual STRI.

- In 2010, Spiegelberg and colleagues conducted a systematic review of studies on HBOT to prevent or treat radiotherapy-induced head and neck injuries associated with treatment of malignant tumors.[55] The authors identified 20 studies. Eight of the studies included control groups; their sample sizes ranged from 19 to 78 individuals. Four (50%) of the studies with a control group concluded that HBOT was effective, and the other 4 did not conclude that the HBOT was effective. The authors noted a paucity of RCTs but did not state the number of RCTs identified in their review.

Randomized Controlled Trials

- Teguh and colleagues reported on 17 patients with oropharyngeal or nasopharyngeal cancer who were treated with radiation therapy.[56] Eight patients were randomly assigned to receive 30 sessions of HBOT, beginning within 2 days of completing radiation therapy, and 9 patients received no additional treatment. All patients were included in the analysis. Quality of life outcomes were assessed and the primary outcome was specified as xerostomia at 1 year. Quality of life measures did not differ significantly between groups in the acute phase (first 3 months). For example, 1 month after treatment, the mean visual analog scale (VAS) score for xerostomia (0-to-10 scale) was 5 in the HBOT group and 6 in the control group. However, at 1 year, there was a statistically significant difference between groups; the mean VAS score for xerostomia was 4 in the HBOT group and 7 in the control group (p=0.002). Also at 1 year, the mean quality of life score for swallowing (0-to-100 scale) was 7 in the HBOT group and 40 in the control group (p=0.0001). The study is limited by the small sample size and the wide fluctuation over the follow-up period in quality-of-life ratings.

- In 2010, Gothard et al. randomized 58 patients with arm lymphedema (at least 15% increase in arm volume) following cancer treatment in a 2:1 ratio to receive HBOT (n=38) or usual care without HBOT (n=20).[57] Fifty-three patients had baseline assessments and 46/58 (79%) had 12-month assessments. No statistically significant difference was found in the change in arm volume from baseline to 12-month follow-up. The median change from baseline was -2.9% in the treatment group and -0.3% in the

control group. The study protocol defined response as at least an 8% reduction in arm volume relative to the contralateral arm. According to this definition, 9 of 30 (30%) patients in the HBOT group were considered responders compared with 3 of 16 (19%) in the control group; the difference between groups was not statistically significant. Other outcomes, e.g., quality-of-life scores on the Short-Form (SF)-36, were also similar between groups.

Conclusion

Due to the lack of sufficient evidence from well-designed clinical trial, HBOT for the treatment of adverse effects related to radiation therapy is considered investigational.

Radionecrosis and Osteoradionecrosis

Several systematic reviews of RCTs have been published. A 2008 Cochrane review by Esposito et al reviewed the use of HBOT in patients requiring dental implants.[29] The authors identified 1 randomized trial involving 26 patients. The authors concluded that despite the limited amount of clinical research available, it appears that HBOT in irradiated patients requiring dental implants may not offer any appreciable clinical benefits. They indicated that there is a need for more RCTs to ascertain the effectiveness of HBOT in irradiated patients requiring dental implants.

In 2012, Bennett et al published a Cochrane review on HBOT for late radiation tissue injury.[58] The authors identified 11 RCTs; there was variability among trials, and study findings were not pooled for the primary outcomes of survival, complete resolution of necrosis or tissue damage, and improvement in a late effects symptom scale. In a pooled analysis of 3 studies, a significantly higher proportion of patients with osteoradionecrosis achieved complete mucosal cover after HBOT compared with controls (RR=1.30; 95% CI, 1.09 to 1.55). From their review of the literature, the authors concluded that data from small trials "suggest that for people with LRTI [late radiation tissue injury] affecting the head, neck, anus, and rectum, [HBOT] is associated with improved outcome. HBOT also appears to reduce the chance of ORN [osteoradionecrosis] following tooth extraction in an irradiated field. There was no such evidence of any important clinical effect on neurological tissues. The application of HBOT to selected patients and tissues may be justified."

Stroke

Current evidence is insufficient to permit conclusions about whether HBOT improves health outcomes in the treatment of stroke or stoke-related functional limitations. The following is a summary of the available evidence:

Acute Stroke

- Systematic Reviews
    - In a 2005 Cochrane systematic review, Bennett and colleagues evaluated HBOT for acute stroke.[59] The investigators identified 6 RCTs with a total of 283 participants that compared HBOT to sham HBOT or no treatment. The authors were only able to pool study findings for 1 outcome, the mortality rate at 3-6 months. A pooled analysis of 3 trials found no significant benefit of HBOT compared to the control for this outcome. Based on the available evidence, acute ischemic stroke is considered investigational

- In a 2005 systematic review, Carson and colleagues concluded that current evidence did not demonstrate any benefit with the use of HBOT for the treatment of stroke.[60] The authors noted it was undetermined whether there were any benefits with HBOT that would outweigh potential harms, and further study was required.

- In a 2014 update of a Cochrane systematic review, Bennett et al evaluated HBOT for acute ischemic stroke. The investigators identified 11 RCTs with a total of 705 participants that compared HBOT with sham HBOT or no treatment. The authors were only able to pool study findings for 1 outcome; mortality at 3 to 6 months. A pooled analysis of data from 4 trials with a total of 106 participants did not find a significant benefit of HBOT compared with a control condition for this outcome (RR=0.97; 95% CI, 0.34 to 2.75).

- Randomized Controlled Trials (RCTs)

  No RCTs have been published since the 2005 systematic reviews.

<u>Stroke-related motor dysfunction</u>

- Randomized Controlled Trials (RCTs)

  In 2013, Efrati and colleagues published an RCT evaluating HBOT for treatment of neurologic deficiencies associated with a history of stroke.[61] The study included 74 patients with at least one motor dysfunction who had an ischemic or hemorrhagic stroke 6-36 months prior to study participation. Participants were randomly assigned to receive 2 months of HBOT (40 daily sessions, 5 days per week, n=30) or delayed treatment (n=32). Patients were evaluated at baseline and 2 months. For patients in the delayed treatment control group, outcomes were evaluated at 4 months after crossing over and receiving HBOT. Twenty-nine of 32 patients (91%) in the delayed treatment group crossed over to the active intervention. Outcome measures included the National Institutes of Health Stroke Scale (NIHSS), which was measured by physicians blinded to treatment group, and several patient-reported quality-of-life and functional status measures.

  At 2 months' follow-up, there was statistically significantly greater improvement in function in the HBOT group compared to the control group as measured by the NIHSS, quality-of-life scales and the ability to perform activities of daily living (ADLs). These differences in outcome measures were accompanied by improvements in single-photon emission computed tomography (SPECT) imaging in the regions affected by stroke. For the delayed treatment control group, there was a statistically significant improvement in function after HBOT compared to before treatment. This RCT raises the possibility that HBOT may induce improvements in function and quality of life for post-stroke patients with motor deficits. However, the results are not definitive for a number of reasons. This RCT is small and enrolled a heterogeneous group of post-stroke patients. The study was not double-blind and the majority of outcome measures, except for the NIHSS, were patient reported and thus prone to the placebo effect. Also, there was a high total dropout rate of 20% at the 2-month follow-up point. Therefore, larger, double-blind studies with longer follow-up are needed to corroborate these results. Because of these limitations in the evidence, HBOT is considered investigational for treating motor dysfunction associated with stroke.

Traumatic Brain Injury

Systematic Review

A 2012 Cochrane systematic review addressed HBOT as adjunctive treatment for traumatic brain injury.[62] The investigators identified 7 RCTs with a total of 571 participants comparing a standard intensive treatment regimen to the same treatment regimen with the addition of HBOT. The review did not include studies in which interventions occurred in a specialized acute care setting. The HBOT regimens varied among studies; for example, the total number of individual sessions varied from 3 to 30-40. No trial used sham treatment or blinded the staff members who were treating the patients, and only 1 had blinding of outcome assessment. Allocation concealment was inadequate in all of the studies. The primary outcomes of the review were mortality and functional outcomes. A pooled analysis of data from 4 trials that reported this outcome found a statistically significantly greater reduction in mortality when HBOT was added to a standard treatment regimen. However, when data from the 4 trials were pooled, the difference in the proportion of patients with an unfavorable functional outcome at final follow-up did not reach statistical significance. Unfavorable outcome was commonly defined as a Glasgow Outcome Score (GOS) of 1, 2 or 3, which are described as ‘dead’, ‘vegetative state’ or ‘severely disabled’. Studies were generally small and were judged to have substantial risk of bias.

Randomized Controlled Trials

A 2012 sham-controlled double-blind trial evaluating HBOT was published after the 2012 Cochrane review.[63] The study included 50 military service members, 48 of whom were male, with combat-related mild traumatic brain injury. Participants were randomized to 30 sessions of HBOT over 8 weeks (n=25) or a sham intervention (room air at 1.3 ATA) (n=25). The primary outcome measures were scores on the Immediate Post-Concussive Assessment and Cognitive Testing (ImPACT) and Post-Traumatic Disorder Check List- Military Version (PCL-M) instruments. Patients were evaluated after every 5 treatment sessions and at 6 weeks post-exposure. Forty-eight of 50 participants (96%) completed the study. There were no statistically significant differences on the ImPACT total mean score or the PCL-M composite score at any time point. While the sample size was relatively small, the study was powered to detect clinically significant differences among groups on the cognitive tests.

Several trials on mild traumatic brain injury in military populations have been published and these did not find significant benefits of HBOT compared with sham treatment. The first trial, published by Wolf et al in 2012, included 50 military service members, 48 of whom were male, with combat-related mild traumatic brain injury. Participants were randomized to 30 sessions of HBOT over 8 weeks (n=25) or a sham intervention (room air at 1.3 atmosphere, absolute [ata]) (n=25). The primary outcome measures were scores on the Immediate Post-Concussive Assessment and Cognitive Testing (ImPACT) and Post- Traumatic Disorder Check List–Military Version (PCL-M) instruments. Patients were evaluated after every 5 treatment sessions and at 6 weeks postexposure. Forty-eight of 50 participants (96%) completed the study. There were no statistically significant differences on the ImPACT total mean score or the PCL-M me point. For example, at the 6-week follow-up, mean composite PCL-M scores were 41.6 in the HBOT group and 40.6 in the sham-control group (p=0.28). While the sample size was relatively small, the study was powered to detect clinically significant differences among groups on the cognitive tests.

A 2014 double-blind sham-controlled trial 2014 RCT by Cifu et al included 61 male Marines who had a history of mild traumatic brain injury and postconcussive syndrome. To maintain blinding, all patients were pressured inside a hyperbaric chamber to 2.0 ata. They were randomized to breathe 1 of 3 oxygen p[nitrogen gas mixes equivalent to: (1) 75% oxygen at 1.5 ata (n=21); (2) 100% oxygen at 2.0 ata (n=19); and (3) sham treatment with surface room air (n=21). Patients underwent 40 once daily 60-minute sessions. Outcomes were assessed 3 months after the last exposure. The primary outcome was a clinically meaningful improvement, defined as a 10% difference between groups in the score on the Rivermead Post-Concussion Questionnaire (RPQ)–16 (scale range, 50-84; higher values indicate more severe symptoms). At follow-up, there was no statistically significant difference among groups on RPQ-16 score (p=0.41). A variety of secondary outcomes were also assessed. None of these, including measures of attention, cognition, or depression, differed significantly among groups at follow-up.

Also in 2014, Miller et al evaluated HBOT in 72 military service members with continuing symptoms at least 4 months after mild traumatic brain injury. Patients were randomized to receive 40 daily HBO sessions at 1.5 ata, 40 sham sessions consisting of room air at 1.2 ata or standard care with no hyperbaric chamber sessions. The primary outcome was change in the RPQ. A cutoff of 15% improvement was deemed clinically important, which translates to a change score of at least 2 points on the RPQ-3 subscale. The proportion of patients who met the prespecified change of at least 2 points on the RPQ-3 was 52% in the HBOT group, 33% in the sham group and 25% in the standard care-only group. The difference between rates in the HBOT and sham groups was not statistically significant (p=0.24). None of the secondary outcomes significantly favored the HBOT group. A criticism of this study, as well as the other military population studies, was that the response in the sham group was not due to a placebo effect but to an intervention effect of slightly increased atmospheric pressure (1.2 ata).43 Other researchers have noted that room air delivered at 1.2 ata would not be considered an acceptable therapeutic dose for any indication, and especially for a condition with persistent symptoms like postconcussive syndrome.

Conclusion

A systematic review of small trials with limitations found a mortality reduction with HBOT but no significant improvement in patient function among survivors of traumatic brain injury. Two double-blind, sham-controlled RCTs of HBO treatment in a military population with mild traumatic brain injury did not find a statistically significant benefit with HBOT. Thus, the evidence is insufficient that HBOT improves health outcomes in patients with traumatic brain injury, and this indication is considered investigational.

Wounds Unrelated to Diabetes

Acute Surgical and Traumatic Wounds

- Systematic Reviews
    - A 2013 updated Cochrane review analyzed randomized controlled trials comparing either HBOT with a different intervention, or two HBOT regimens for acute wounds (e.g., surgical wounds, lacerations, traumatic wounds, and animal bites).[64] The four studies that met inclusion criteria ranged in size from 10 to 135 subjects. Reported outcomes were mixed. Meta-analysis of pooled data was not possible due to differences among studies with respect to patient characteristics, interventions

studied, and outcome measures. Also identified was a high risk of bias due to insufficient disclosure of randomization methods and selective reporting of outcome data. Findings of individual studies were mixed.

The primary outcome examined by Cochrane reviewers, wound healing was not reported in either of the 2 trials comparing HBOT with usual care[65,66] or in the 1 trial comparing HBOT with dexamethasone or heparin.[67] Complete wound healing was reported in the 1 RCT comparing active HBOT with sham HBOT.[68] In this small study (n=36), there was a statistically higher rate of wound healing in the active HBOT group. The time point for outcome measurement in this study was unclear, but there was no statistically significant difference between groups in the meantime to wound healing. Adverse effects included 2 additional surgical procedures in 1 patient in the HBOT group compared with 8 in 6 patients in the sham group. The HBOT group had significantly fewer patients who developed necrotic tissue (1 and 8, respectively). There were no amputations in the HBOT group compared with 2 amputations in the sham group, but this difference did not reach statistical significance. The authors concluded that evidence remains insufficient to support the routine use of HBOT for acute surgical or traumatic wounds. They recommended further evaluation in high quality RCTs that include outcomes measures of complete wound closure and accelerated wound closure.

- In 2014 Dauwe et al. published a systematic review that included 8 studies with sample sizes ranging from 5 to 125 patients. Four studies were randomized, 3 were prospective non-RCTs, and 1 was a retrospective non- RCT. Data were not pooled due to the heterogeneity described below. The authors noted that 7 of the 8 studies reported achieving statistical significance in their primary end points, but the end points differed among studies (eg, graft survival, length of hospital stay, wound size). Moreover, the studies were heterogeneous in terms of treatment regimens, patient indications (eg, burns, face lifts), and study designs, making it difficult to draw conclusions about the effect of HBOT on acute wound treatment.

- Randomized Controlled Trials (RCTs)

  No RCTs have been published since those included in the systematic reviews summarized above.

Chronic Non-diabetic Wounds

- Systematic Reviews

  Several systematic reviews of RCTs have been published. An updated 2007 Cochrane review of randomized controlled trials (RCTs) on HBOT for chronic wounds was published by Kranke and colleagues in 2012.[69] The authors identified 9 RCTs with a total of 471 participants that compared the effect of HBOT on chronic wound healing compared with an alternative treatment approach that did not use HBOT. Eight of the 9 trials included in the review evaluated HBOT in patients with diabetes. The remaining trial addressed HBOT for patients with venous ulcers; that study had only 16 participants and the comparator treatment was not specified. In a pooled analysis of data from 3 trials, a significantly higher proportion of ulcers had healed at the end of the treatment period (6 weeks) in the group receiving HBOT compared to the group not receiving HBOT (RR: 5.20: 95% CI: 1.25 to 21.7). Pooled analyses, however, did not

find significant differences between groups in the proportion of ulcers healed in the HBOT versus non-HBO-treated groups at 6 months (2 trials) or 12 months (3 trials). There were insufficient data to conduct pooled analyses of studies evaluating HBOT for treating patients with chronic wounds who did not have diabetes.

In 2013, O'Reilly et al[70] published a systematic review of studies on HBOT for treatment of diabetic ulcers. The authors identified 6 RCTs and 6 non-RCTs that compared HBOT with standard wound care or sham therapy in patients with diabetes who had nonhealing lower-limb ulcers. Pooled analyses of observational studies found statistically significant benefits of HBOT on rates of major amputation, minor amputation and the proportion of wounds healed at the end of the study period. However, in pooled analyses of RCT data, the stronger study design, there were no statistically significant differences between groups on key outcomes. This included the rate of major amputation (RR=0.40; 95% CI, 0.07 to 2.23; p=0.29), minor amputation (RR=0.79; 95% CI, 0.19 to 3.30, p=0.75), and the proportion of unhealed wounds at the end of the study period (RR=0.54, 95% CI, 0.26 to 1.13, p=0.1).

Systematic reviews have had mixed findings on the impact of HBOT on diabetic ulcers. A Cochrane review found short-term, but not long-term benefit on wound healing, and a 2013 meta-analysis did not find significant benefits of HBOT on outcomes in RCTs, but did find an effect in non-RCTs. There is insufficient evidence on HBOT for treatment of chronic wounds in patients without diabetes.

- Randomized Controlled Trials (RCTs)

  No RCTs have been published since those included in the systematic reviews summarized above.

- Conclusion

  Published clinical trial data is insufficient to determine the effectiveness of HBOT for wounds that are not related to diabetes. The UHMS does not include these wounds in their list of indications for HBOT, noting the lack of available evidence.[71] As shown in studies of adjunctive HBOT for treatment of severe diabetic lower extremity ulcers, this treatment is well suited to randomized, controlled comparative trials. In spite of this, only 1 small (n=16) randomized, controlled trial was found for non-diabetic wounds.[72] This trial is too small and short-term to be reliable.

Other Indications

No data from well-designed randomized, controlled clinical trials were found that supported HBOT for any other investigational indication, including but not limited to refractory mycoses and acute peripheral arterial insufficiency.

Other indications

For the indications listed below, insufficient evidence to support the use of HBOT was identified. Since 2000, there have been no published controlled trials or large case series (i.e., ≥ 25 patients):

- bone grafts;

- carbon tetrachloride poisoning, acute;
- cerebrovascular disease, acute (thrombotic or embolic) or chronic;
- fracture healing;
- hydrogen sulfide poisoning;
- intra-abdominal and intracranial abscesses;
- lepromatous leprosy;
- meningitis;
- pseudomembranous colitis (antimicrobial agent-induced colitis);
- radiation myelitis;
- sickle cell crisis and/or hematuria;
- amyotrophic lateral sclerosis;
- retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment;
- pyoderma gangrenosum;
- tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy;

SUMMARY OF EVIDENCE

There is sufficient published evidence to determine that use of hyperbaric oxygen therapy (HBOT) in selected patients with nonhealing diabetic wounds of the lower extremities, acute traumatic ischemia, soft-tissue radiation necrosis (eg, radiation enteritis, cystitis, proctitis), osteoradionecrosis (ie, pre- and posttreatment) for patients undergoing dental surgery (non-implant-related) of an irradiated jaw, gas gangrene, and profound anemia with exceptional blood loss when blood transfusion is impossible or must be delayed improves the net health outcome. There is insufficient evidence for patients all other indications included in the Rationale section that HBOT improves the net health outcome.

PRACTICE GUIDELINE SUMMARY

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

In 2013, the FDA published a position statement with a warning that HBOT has not been proven safe and effective for uses not cleared by the agency.[1] This statement was developed due to numerous complaints from consumers and health care professionals that unproven claims made by some HBOT centers may mislead consumers and ultimately endanger their health. The statement included the following conditions for which patients may be unaware that safety and effectiveness of HBOT have *not* been established:

- AIDS/HIV

- Alzheimer's Disease
- Asthma
- Bell's Palsy
- Brain Injury
- Cerebral Palsy
- Depression
- Heart Disease
- Hepatitis
- Migraine
- Multiple Sclerosis
- Parkinson's Disease
- Spinal Cord Injury
- Sport's Injury
- Stroke

UNDERSEA AND HYPERBARIC MEDICAL SOCIETY (UHMS)

In 2015, the Undersea and Hyperbaric Medical Society (UHMS) published a guideline on the use of HBOT for treatment diabetic foot ulcers.[73,74] Recommendations are as follows:

- Suggest against using HBOT in patients with Wagner Grade 2 or lower diabetic foot ulcers
- Suggest adding HBOT in patients with Wagner Grade 3 or higher diabetic foot ulcers that have now shown significant improvement after 30 days of standard of care therapy
- Suggest adding acute post-operative HBOT to the standard of care in patients with Wagner Grade 3 or higher diabetic foot ulcers who have just had foot surgery related to their diabetic ulcers.

- Appropriate Indications for HBOT[75]

  In 2014, the UHMS updated their list of indications considered *appropriate* for hyperbaric oxygen therapy. These indications are as follows:

  - Acute thermal burn injury
  - Air or gas embolism
  - Arterial insufficiencies (central retinal artery occlusion; enhancement of healing in selected problem wounds)
  - Carbon monoxide poisoning and carbon monoxide poisoning complicated by cyanide poisoning
  - Clostridial myositis and myonecrosis (gas gangrene)
  - Compromised grafts and flaps
  - Crush injury, compartment syndrome, and other acute traumatic ischemias
  - Decompression sickness
  - Delayed radiation injury (soft tissue and bony necrosis)
  - Intracranial abscess
  - Idiopathic sudden sensorineural hearing loss (ISSNHL) (patients with moderate to profound ISSNHL who present within 14 days of symptom onset)
  - Necrotizing soft tissue infections
  - Osteomyelitis (refractory)

- Severe anemia

- Autism Spectrum Disorder (ASD)[13]

  The 2009 UHMS position paper included a critical appraisal of the available literature, in particular the 2009 Rossignol et al. RCT[11] which was the only RCT available at that time. The paper concluded that "the UHMS cannot recommend the routine treatment of ASD with HBO_2T outside appropriate comparative research protocols."

- Chronic Brain Injury[76]

  The most recent UHMS position statement on chronic brain injury (e.g., traumatic brain injury, cerebral palsy, stroke) is from 2003. The statement considered the evidence to be insufficient to support a recommendation for HBOT for the chronic sequelae of traumatic or non-traumatic brain injury, but noted that continued monitoring of data is warranted.

- Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL)[77]

  In October 2011, the UHMS Executive Board approved ISSNHL as an additional indication. According to treatment guidelines, patients with moderate to profound ISSNHL who present within 14 days of symptom onset should be considered for HBOT treatment.

- Multiple Sclerosis[47]

  A 2010 UHMS position paper reported that most RCTs have failed to show clinical benefit for HBOT therapy for multiple sclerosis. "We conclude that, while there is some case for further investigation of possible therapeutic effects in selected sub-groups of patients (well-characterized and preferably early in the disease course) and for the response to prolonged courses of HBOT, this case is not strong. At this time, the UHMS cannot recommend the routine treatment of MS with HBOT outside appropriate comparative research protocols."

- Topical Oxygen for Chronic Wounds [78]

  A 2005 UHMS position statement reported that, "to date, mechanisms of action whereby topical oxygen might be effective have not been defined or substantiated. Conversely, cellular toxicities due to extended courses of topical oxygen have been reported, although, again these data are not conclusive, and no mechanism for toxicity has been examined scientifically...The only randomized trial for topical oxygen in diabetic foot ulcers actually showed a tendency toward impaired wound healing in the topical oxygen group. Contentions that topical oxygen is superior to hyperbaric oxygen are not proven." Therefore, the UHMS recommends against application of topical oxygen outside a clinical trial setting, noting that topical oxygen "should be subjected to the same intense scientific scrutiny to which systemic hyperbaric oxygen has been held."

NATIONAL BOARD OF DIVING & HYPERBARIC MEDICAL TECHNOLOGY[7]

As noted above, the current position statement concluded that "the installation and provision of in-home hyperbaric oxygen therapy is inherently unsafe and cannot be condoned." This position is based on concern for the safety and well-being of patients as well as those people in proximity to the HBOT delivery system because in-home provision of HBOT is likely to:

1. Bypass otherwise mandatory federal, state, and local codes related to design, construction, installation, and operation of these devices; and
2. Occur without adequate physician oversight and the operational support of appropriately qualified HBOT providers.

AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY (AAO-HNS)[79]

In 2012, the AAO-HNS published an evidence-based clinical practice guideline on treatment of sudden hearing loss. The guideline includes a statement that HBOT may be considered a treatment option for patients who present within 3 months of a diagnosis of idiopathic sudden sensorineural hearing loss. The document states, “Although HBOT is not widely available in the United States and is not recognized by many U.S. clinicians as an intervention for ISSNHL, the panel felt that the level of evidence for hearing improvement, albeit modest and imprecise, was sufficient to promote greater awareness of HBOT as an intervention for [this condition]” The strength of the recommendation was rated “Option” defined in this case as based on systematic reviews of RCTs with a balance between benefit and harm.

SUMMARY

Hyperbaric oxygen therapy (HBOT) has been studied for a wide variety of clinical indications. There is enough evidence to show that HBOT is safe and effective for a variety of indications. There are guidelines based on research that recommend the use of HBOT for a variety of indications. Therefore, the use of HBOT may be considered medically necessary when policy criteria are met.

For the investigational indications discussed in the policy, the evidence is not sufficient to permit conclusions concerning the effects of HBOT on final health outcomes. Therefore, these indications are considered investigational.

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CODES

Codes	Number	Description
CPT	99183	Physician or other qualified health care professional attendance and supervision of hyperbaric oxygen therapy, per session Note: This code is not intended for reporting systemic oxygen therapy in chambers that provide oxygen at less than hyperbaric pressure (eg, “mild hyperbaric” oxygen therapy) which should be reported using code 99199.
	99199	Unlisted special service, procedure or report
HCPCS	A4575	Topical hyperbaric oxygen chamber, disposable

Codes	Number	Description
	E0446	Topical oxygen delivery system, not otherwise specified, includes all supplies and accessories NOTE: This code is intended for devices such as the TransCu 02 that deliver oxygen at normal atmospheric pressure under wound dressings; it should not be used to report topical hyperbaric oxygen therapy devices.
	E1399	Durable medical equipment, miscellaneous
	G0277	Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval

Date of Origin: *January 1996*