IBD REVIEWS

Scientific and technological research article

Hyperbaric oxygen therapy and inflammatory bowel disease

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Hyperbaric oxygen therapy and IBD

Resumen

La enfermedad inflamatoria intestinal (EII), incluida la colitis ulcerosa (CU) y la enfermedad de Crohn (EC), es un grupo de enfermedades crónicas recurrentes caracterizadas por una inflamación crónica del tracto gastrointestinal. La prevalencia de la EII está aumentando a nivel mundial y, en las últimas décadas, se lograron mejoras significativas en las opciones terapéuticas que han reducido la necesidad de hospitalización y cirugía. Sin embargo, incluso con estrategias de tratamiento médico óptimas, los pacientes con EC pueden experimentar progresión de la enfermedad con complicaciones perianales, intestinales y extraintestinales. Además, una cuarta parte de los pacientes con CU desarrollará una exacerbación aguda grave de la enfermedad durante su vida. A pesar de las altas dosis de corticosteroides, la mitad de estos pacientes fracasará en la terapia de rescate médico posterior y la otra mitad necesitará colectomía dentro de los 5 años. Se ha sugerido la terapia con oxígeno hiperbárico (TOHB) como un posible tratamiento complementario para los pacientes que padecen enfermedad inflamatoria intestinal. El propósito de esta revisión es resumir la función de TOHB en el tratamiento de la EII.

Palabras clave: Enfermedad de Crohn, Colitis ulcerosa, Oxigenoterapia hiperbárica, intestino inflamatorio.

Abstract

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a group of chronic recurrent diseases characterized by chronic inflammation of the gastrointestinal tract. The prevalence of IBD is increasing globally and, in the past few decades, significant improvements were made in therapeutic options which have reduced the need for hospitalization and surgery. However, even with optimal medical therapy strategies, patients with CD may experience disease progression with perianal, intestinal, and extraintestinal complications. In addition, one quarter of patients with UC will develop a severe acute exacerbation of disease during their lifetime. Despite high dose corticosteroids, half of these patients will fail subsequent medical rescue therapy, and half will require colectomy within 5 years. Hyperbaric oxygen therapy (HBOT) has been suggested as a potential adjunctive treatment for patients suffering from inflammatory bowel disease. The purpose of this review is to summarize the role of HBOT in the treatment of IBD.

Keywords: Crohn's disease, Ulcerative colitis, Hyperbaric oxygen therapy, inflammatory bowel Diseases.

INTRODUCTION

Over the past few decades, the treatment of inflammatory bowel disease (IBD) has made great progress. However, there are many refractory patients that do not respond to treatment. Hyperbaric oxygen therapy (HBOT) has been suggested as a potential adjunctive treatment for patients suffering from IBD (1-5).There is a subset of patients with IBD that may have benefits of use of HBOT, especially patients with severe ulcerative colitis (UC) (6-9), refractory Crohn's disease (CD) (2) and patients with complications of CD and UC, such as pyoderma gangrenosum (2,10), enterocutaneous fistula (2), complex perianal fistula (11-13), fistulizing pouch complications (14), and metastatic CD (15). HBOT is safe and well tolerated (16). The purpose of his review is to summarize the use of HBOT in IBD and to provide a review of the literature.

MECHANISM OF ACTION OF HYPERBARIC OXYGEN THERAPY IN INFLAMMATORY BOWEL DISEASES

HBOT is defined as the therapeutic effect of inhaling 100% oxygen higher than one atmosphere. Usually, patients with IBD that are eligible for HBOT are treated with 20-60 daily hyperbaric oxygen sessions, and each session consists of administration of a total of 80-90 minutes of 100% oxygen at 243#253 kilopascal, as describe elsewhere (11). The hyper oxygenation and oxidative stress associated with HBOT has been shown to result in anti#inflammatory effects (17). Hypoxia has been shown to activate multiple inflammatory mechanisms that are associated with inflammation. It is proposed that hypoxia and an inappropriate mucosal immune response to normal intestinal constituents are key factors that lead to an imbalance in local pro- and anti-inflammatory cytokines, including a high concentration of tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) and increased expression of hypoxia-inducible factor 1alpha (HIF-1α). (17) It was previously showed that HBOT therapy attenuates the severity of acute distal colitis, with reduced macroscopic damage score. This effect was associated with prevention in the increase of pro-inflammatory cytokine production; myeloperoxidase activity, in the expression of inducible nitric oxide synthase and cyclooxygenase-2. HBOT might be through down-regulation of HIF-1α expression (17). HBOT not only improves plasma and tissue oxygen content but also improves the oxygen levels of blood reaching inflamed bowel.

HYPERBARIC OXYGEN THERAPY AND ULCERATIVE COLITIS

HBOT has been demonstrated to be effective for UC therapy. Indeed, several clinical trials have suggested that HBOT is effective for UC therapy, (7, 9, 18) and a recent review summarizes the clinical evidence for this indication

(19). The mechanism of action of HBOT for UC could be associated with reduction of pro-inflammatory cytokines and chemokines which are responsible for the metabolic stress created during active inflammation. One study focused on the therapeutic potential of HBOT as an adjunct to steroids for UC flares requiring hospitalization (7). The authors showed that a significantly higher proportion of HBOT-treated patients achieved clinical remission at study day 5 and 10 (50 vs. 0%, p = 0.04) compared to the group that received sham treatment. HBOT-treated patients also less often required progression to second-line therapy during the hospitalization (10 vs. 63%, p = 0.04). The proportion requiring in-hospital colectomy specifically as second-line therapy for medically refractory UC was lower in the HBOT group (0 vs. 38%, p = 0.07). There were no serious adverse events. A limitation to this study is that it included a small number of patients (n=18), however, in this phase 2A trial, the use of HBOT as an adjunctive therapy to steroids for UC patients hospitalized for moderate-severe flares resulted in higher rates of clinical remission, and a reduction in rates of progression to second-line therapy during the hospitalization. The same group recently published a phase 2B randomized trial of hyperbaric oxygen therapy for ulcerative colitis patients hospitalized for moderate to severe flares (9). The authors treated 20 patients with hyperbaric oxygen (75% prior biologic failure). Day 3 response was achieved in 55% (n = 11/20), with significant reductions in stool frequency, rectal bleeding and CRP (P < 0.01). A more significant reduction in disease activity was observed with 5 days vs 3 days of hyperbaric oxygen (P = 0.03). Infliximab or colectomy was required in only three patients (15%) despite a predicted probability of 80% for second-line therapy. Day 3 hyperbaric oxygen responders were less likely to require re-hospitalization or colectomy by 3 months vs non-responders (0% vs 66%, P = 0.002). No treatment-related adverse events were observed. Hyperbaric oxygen appears to be effective for optimizing response to intravenous steroids in UC patients hospitalized for acute flares, with low rates of re-hospitalization or colectomy at 3 months. An optimal clinical response is achieved with 5 days of HBOT.

HYPERBARIC OXYGEN THERAPY AND CROHN'S DISEASE

The largest number of patients with CD treated with HBOT and published in the English language was recently published (2). The authors studied 40 patients with CD and observed that adjunctive HBOT was associated with high rates of complete healing of CD-related complications, such as perianal CD, enterocutaneous fistulas, and pyoderma gangrenosum, without the need for invasive surgical procedures and with adequate safety, as no HBOT-related adverse events were observed. Other authors accessed the efficacy, safety and feasibility of HBOT in patients with CD with therapy-refractory perianal fistulas (11). Seven women and 13 men were included (median age 34 years). At Week 16, median scores of perianal disease activity index and modified van Assche index (co-primary outcome parameters) decreased from 7.5 (95% CI 6-9) to 4 (95% CI 3-6, P < 0.001), and from 9.2 (95% CI 7.3-11.2) to 7.3 (95% CI 6.9-9.7, P = 0.004) respectively. Perianal disease activity index scores ≤4 (representing inactive perianal disease) were observed in 13/20 patients (65%). Twelve patients showed a clinical response (60%) and four (20%) clinical remission, assessed with fistula drainage assessment. Median C-reactive protein and faecal calprotectin levels decreased from 4.2 mg/mL (95% CI 1.6-8) to 2.2 (95% CI 0.9-4.3, P = 0.003) and from 399 µg/g (95% CI 52-922) to 31 (95% CI 16-245, P = 0.001), respectively. The authors found significant clinical, radiological and biochemical improvement in CD patients with therapy-refractory perianal fistulas after treatment with HBOT.

A prospective study, consecutive CD patients presenting with rectovaginal fistulas (12). Out of 14 eligible patients, nine patients (median age 50 years) were treated, all of whom had previously had one or more unsuccessful medical and/or surgical treatments for their RVF. Clinical closure occurred in none of the patients at 3-month follow-up. There was no improvement in PDAI and patient-reported outcomes (VAS, IBDQ, FIQL and FSFI). Two patients had concomitant perianal fistulas; using FDA, one patient had a clinical response and one patient was in clinical remission 3 months after HBO. There were two treatment-related adverse events during HBO concerning claustrophobia and fatigue. Furthermore, two patients had a surgical intervention due to RVF and two patients were treated with antibiotics for a urinary tract infection during follow-up. One patient had a dose reduction of ustekinumab because of decreased luminal complaints. Treatment with HBO was feasible, but in this therapy-refractory cohort without deviating ostomy no clinical closure of RVF or improvement in quality of life was seen 3 months after HBO. Treatment with HBO alone in this specific group of patients therefore appears to be ineffective, but given the good results in other phenotypes of Crohn's disease, different treatment strategies (e.g. treatment of patients with ostomy or in combination with an attempt at surgical closure) could be explored in the future.

CONCLUSIONS

Current standard care options are not always sufficient for the adequate treatment of IBD patients. Hyperbaric oxygen therapy has been suggested as an (adjuvant) treatment option, and multiple recent studies have shown positive effects after HBOT. Especially patients that are hospitalized with a moderate to severe flare of ulcerative colitis, or Crohn's disease patients with complications such pyoderma gangrenosum or fistulas seem to benefit, although a recent trial did not show any effect on rectovaginal Crohn's fistulas. Future larger, controlled trials are warranted in order to further substantiate the evidence and, in case of confirmation of positive outcomes, to allow hyperbaric oxygen therapy to become part of standard care for these patient groups.

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