CASE REPORT

Hyperbaric oxygen therapy for chronic antibiotic-refractory ischemic pouchitis

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Abstract

Hyperbaric oxygen therapy (HBOT) has been shown to be efficacious in treating various conditions, including perianal Crohn's disease. Here we present a case of a 59-year-old male with a history of ulcerative colitis, who underwent a total proctocolectomy and two-stage J-pouch construction. He later developed chronic antibiotic-refractory pouchitis with endoscopic features of ischemia. At the completion of HBOT—a total of 20 sessions of 100% oxygen at 3.0 atmospheres absolute for 90-90 minutes per session—a repeat pouchoscopy showed marked improvement of endoscopic mucosal inflammation. HBOT is known to increase tissue oxygenation, reduce tissue hypoxia, alter inflammatory pathways and promote tissue healing. This case demonstrated the therapeutic role of HBOT as well as the possible disease mechanism in chronic antibiotic-refractory pouchitis.

Key words: hyperbaric oxygen therapy; refractory pouchitis; ischemic pouchitis

Introduction

Hyperbaric oxygen therapy (HBOT) has been found to be safe and efficacious in treating various conditions, including inflammatory bowel disease (IBD) [1]. The therapy has gained favor as a first-line and/or adjuvant therapy in the treatment of carbon monoxide cyanide poisoning, decompression sickness, air embolism, acute ischemic injuries and radiation injury [2]. More recently, its application to non-healing ulcers, skin grafts and wounds has also been described [3]. Studies have proven the safety of HBOT in the treatment of IBD, especially perianal Crohn’s disease (CD), but the efficacy of the therapy is yet to be validated through randomized, controlled trials [1]. The mechanism of the therapy is thought to be through the increase in tissue oxygenation, leading to changes in inflammatory and tissue repair pathways [2, 4]. Conditions that include tissue ischemia have been shown to improve under HBOT therapy; these findings led our group into postulating the potential benefits of HBOT in patients with chronic antibiotic-refractory pouchitis (CARP) with endoscopic features of ischemia.

Case presentation

The patient was a 59-year-old male who presented to our Pouch Center with recalcitrant pouchitis, characterized by bowel frequency, hematochezia, urgency, lower abdominal pain and nocturnal incontinence. He was a former-smoker (15-pack-years) with previous medical history of perforated diverticulitis in 2001. He was later diagnosed as having ulcerative colitis (UC) in 2007. He developed steroid-refractory UC, which necessitated surgical intervention with total proctocolectomy and a two-stage J-pouch construction in the same year. The patient remained asymptomatic following closure of the ileostomy but developed an incisional hernia 1.5 years later, which was repaired laparoscopically with mesh placement. He later developed increased bowel...
Acute, hemorrhagic, a burning sensation with bowel movements and bowel incontinence. He was diagnosed with pouchitis and treated with ciprofloxacin. In 2013, his symptoms progressively worsened, with increased lower abdominal pain and bleeding. He was treated with metronidazole and started on mesalamine suppositories. He continued to be symptomatic and additional treatment with hydrocortisone rectal foam for two weeks could not alleviate his symptoms. Pouchoscopy was performed, which showed ulcerated and nodular mucosa at the distal 10 cm of the pouch limb side of the pouch body, the pattern consistent with ischemic pouchitis (Figure 1). HBOT was recommended, based on the fact that his symptoms persisted despite therapy with anti-inflammatory drugs and antibiotics and the distribution pattern of mucosal inflammation suggestive of ischemia. The patient underwent HBOT—30 sessions of 100% oxygen at 2.5–3.0 atmospheres absolute (ATA) for 60–90 min each, in addition to continuing on mesalamine and hydrocortisone rectal foam. Seven weeks after this follow-up pouchoscopy revealed an approximately 65% resolution of the gross inflammation and improvement of clinical symptoms (Figure 2).

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References

Hyperbaric oxygen treatment for inflammatory bowel disease: a systematic review and analysis

Daniel A Rossignol

Abstract

Background: Traditionally, hyperbaric oxygen treatment (HBOT) has been used to treat a limited repertoire of disease, including decompression sickness and healing of problem wounds. However, some investigators have used HBOT to treat inflammatory bowel disease (IBD), including Crohn’s disease and ulcerative colitis.

Methods: Comprehensive searches were conducted in 8 scientific databases through 2011 to identify publications using HBOT in IBD. Human studies and animal models were collated separately.

Results: Thirteen studies of HBOT in Crohn’s disease and 6 studies in ulcerative colitis were identified. In all studies, participants had severe disease refractory to standard medical treatments, including corticosteroids, immunomodulators and anti-inflammatory medications. In patients with Crohn’s disease, 31/40 (78%) had clinical improvements with HBOT, while all 39 patients with ulcerative colitis improved. One study in Crohn’s disease reported a significant decrease in proinflammatory cytokines (IL-1, IL-6 and TNF-alpha) and one study in ulcerative colitis reported a decrease in IL-6 with HBOT. Adverse events were minimal. Twelve publications reported using HBOT in animal models of experimentally-induced IBD, including several studies reporting decreased markers of inflammation or immune dysregulation, including TNF-alpha (3 studies), IL-1beta (2 studies), neopterin (1 study) and myeloperoxidase activity (5 studies). HBOT also decreased oxidative stress markers including malondialdehyde (3 studies) and plasma carbonyl content (2 studies), except for one study that reported increased plasma carbonyl content. Several studies reported HBOT lowered nitric oxide (3 studies) and nitric oxide synthase (3 studies) and one study reported a decrease in prostaglandin E2 levels. Four animal studies reported decreased edema or colonic tissue weight with HBOT, and 8 studies reported microscopic improvements on histopathological examination. Although most publications reported improvements with HBOT, some studies suffered from limitations, including possible publication and referral biases, the lack of a control group, the retrospective nature and a small number of participants.

Conclusions: HBOT lowered markers of inflammation and oxidative stress and ameliorated IBD in both human and animal studies. Most treated patients were refractory to standard medical treatments. Additional studies are warranted to investigate the effects of HBOT on biomarkers of oxidative stress and inflammation as well as clinical outcomes in individuals with IBD.

Keywords: Hyperbaric oxygen treatment, Inflammation, Oxidative stress, Inflammatory bowel disease, Crohn’s disease, Ulcerative colitis, Biomarkers

Background

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal (GI) tract characterized by chronic and recurrent ulcerations [1], and includes Crohn’s disease and ulcerative colitis. IBD is usually accompanied by severe GI symptoms such as diarrhea, bleeding, abdominal pain, weight loss, and anemia. The symptoms of IBD can be intermittent, with periods of exacerbations and periods that may be relatively free of symptoms. Recent evidence suggests that the pathophysiology of IBD involves immune dysregulation, genetic susceptibilities, intestinal barrier dysfunction, and alterations in microbial flora [2]. Activated macrophages appear to play a key role in the disease process and produce proinflammatory cytokines,
including TNF-α and interleukins (IL-6 and IL-8) [3]. Intestinal nitric oxide (NO) levels are also increased in some patients with IBD which may lead to increased intestinal tissue injury [4]. Oxidative stress and mitochondrial dysfunction are also found in some patients with IBD [5,6]. Some investigators have reported that certain infections such as Mycobacterium avium subspecies paratuberculosis may also play a role in IBD [7]. Interestingly, decreased blood flow to the rectum has been reported in some individuals with ulcerative colitis [8].

Current medical treatments for IBD are aimed at maintaining clinical remission and include biologic therapies (e.g., monoclonal antibodies), immunomodulators, aminosalicylates, corticosteroids and other anti-inflammatory modalities [9]. Several studies have reported improvements using hyperbaric oxygen treatment (HBOT) in some patients with IBD [10−12]. HBOT involves inhaling 100% oxygen at greater than one atmosphere absolute (ATA) in a pressurized chamber [13]. HBOT has been used successfully in humans at varying pressures to treat a range of conditions. Many clinical applications of HBOT are at higher pressures (e.g., 2.0 ATA and above) including treatment of decompression sickness, arterial gas embolism, and carbon monoxide poisoning [14]. HBOT has been shown to increase the oxygen content of plasma [15] and body tissues [16] and may normalize oxygen levels in ischemic tissues [17]. Recently, evidence has accumulated that HBOT also has potent anti-inflammatory effects [18−20]. This manuscript is a systematic review and analysis of the medical literature concerning the use of HBOT in IBD.

Methods
Search strategy
A search of the Pubmed, EMBASE, Google Scholar, CINAHL, ERIC, AMED, PsychINFO, and Web of Science databases from their inception through December 31, 2011 was conducted to identify and collate pertinent publications using the search terms "hyperbaric oxygen," "HBOT," "hyperbaric" in all combinations with "IBD," "inflammatory bowel," "inflammatory bowel disease," "colitis," "ulcerative colitis," "Crohn’s," "Crohn’s," "esophagitis," "gastritis," "duodenitis," "jejunitis," "ileitis," and "proctitis." Figure 1 demonstrates the flow chart of publications identified by the literature search.

Study selection
Publications were initially included if they: (1) involved individuals or specimens from individuals with IBD (including Crohn’s disease and ulcerative colitis) or were animal models of IBD, and (2) reported using HBOT. Abstracts of identified publications were reviewed to determine if a publication should be included. If the abstract was obscure or missing, the publication was reviewed to determine if inclusion was warranted. Publications of animal models were collated separately. Studies of gastrointestinal abnormalities caused exclusively by radiation treatment were excluded (36 studies). Studies not written in English (9 studies) [21−29] were excluded (unless an English abstract was available). Studies that were purely review articles (4 studies) [30−33] or letters to the editor (3 publications) [34−36] that did not present any new or unique data were also excluded. Finally, studies that published repeated data and not new or unique data (2 studies) [37,38] were excluded.

Results
Publications identified by the search
A total of 466 publications were identified. After 233 duplicates were removed, 233 publications were examined. Studies meeting inclusion criteria included 13 publications on the use of HBOT in Crohn’s disease, 6 on ulcerative colitis and 12 on animal models of IBD.

Studies on Crohn’s disease
Table 1 outlines the 13 studies [10,11,39−49] meeting inclusion criteria that reported the use of HBOT in Crohn’s disease. Six studies were prospective [10,41−43,47,49] and one contained a control group [49]. In each of the 13 studies, the patients had severe Crohn’s disease that was refractory to standard medical treatments, including in some cases, corticosteroids, sulfasalazine, metronidazole, 6-mercapto- purine, and an elemental diet. One study reported improvements with a stay of up to 3 weeks at the Dead Sea (equivalent to 1.05 ATA) in 6 patients [42]. Two studies
## Table 1: Studies of HBOT in Crohn's disease

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Type of study</th>
<th>Number of patients improved/number treated</th>
<th>Location</th>
<th>HBOT parameters</th>
<th>Side effects</th>
<th>Comments/outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brady et al. 1989 [39], USA</td>
<td>Case report</td>
<td>1/1</td>
<td>Perineal, cutaneous</td>
<td>2.4 ATA 100% oxygen; 6 days a week; 2 h sessions; 67 total sessions</td>
<td>Blurred vision, resolved</td>
<td>Crohn's disease was refractory to surgery and medical treatment (corticosteroids, sulfasalazine, metronidazole, and 5-mercaptopurine) for 8 years; complete and dramatic healing in 2.5 months with HBOT; patient needed additional HBOT over 11 months, then had lasting improvements</td>
</tr>
<tr>
<td>Brady 1993 [40], USA</td>
<td>Letter to editor/case report</td>
<td>1/1</td>
<td>Perineal, cutaneous</td>
<td>Not reported, but presumably the same as previous report (Brady et al. 1989) [39]</td>
<td>NR</td>
<td>Update on patients from previous case report (Brady et al. 1989) [39]; patients had two additional courses of HBOT (29 and 26 sessions) and were in remission for over 3 years at time of letter</td>
</tr>
<tr>
<td>Colombel et al. 1995 [41], France</td>
<td>Prospective, uncontrolled</td>
<td>6/10</td>
<td>Perineal</td>
<td>2.5 ATA 100% oxygen; 2 sessions per day; 5 sessions per week; 40 planned sessions over 4 weeks; 8 patients completed at least 20 treatments</td>
<td>1 patient had bilateral ear drum perforation; another had psychological intolerance</td>
<td>All patients had severe Crohn's disease and had failed one or more standard medical treatments; 2 patients stopped treatments after a few sessions due to side effects; 6 of 8 fully treated patients had partial or complete healing</td>
</tr>
<tr>
<td>Fraser and Niv 1995 [42], Israel</td>
<td>Prospective, uncontrolled</td>
<td>6/6</td>
<td>Perianal, Ileocele</td>
<td>Equivalent to 1.05 ATA</td>
<td>NR</td>
<td>6 patients with Crohn's disease unresponsive to standard medical treatments spent up to 3 weeks at the Dead Sea; significant healing noted in all 6 patients</td>
</tr>
<tr>
<td>Ipez et al. 2011 [43], Brazil</td>
<td>Prospective, uncontrolled</td>
<td>11/14</td>
<td>Perineal or cutaneous</td>
<td>2.4 ATA; 2 h sessions; 1 session per day; 10-50 total sessions</td>
<td>NR</td>
<td>Patients had Crohn's disease refractory to standard medical treatments; 11 of 14 (79%) had &quot;satisfactory improvement&quot; (complete or partial improvement) with HBOT</td>
</tr>
<tr>
<td>Jiang et al. 2000 [44], USA</td>
<td>Case report</td>
<td>1/1</td>
<td>Ileocele</td>
<td>2.5 ATA 100% oxygen; 90 min sessions; 28 day duration</td>
<td>NR</td>
<td>Patient had Crohn's disease and Clostridium septicum infection, treated with antibiotics and HBOT postoperatively with improvements noted</td>
</tr>
<tr>
<td>Kael et al. 2011 [45], Australia</td>
<td>Case report</td>
<td>1/1</td>
<td>Cecal</td>
<td>NR</td>
<td>NR</td>
<td>Patient had Crohn's disease and Clostridium septicum infection, treated with antibiotics and HBOT postoperatively with improvements noted</td>
</tr>
<tr>
<td>Levy et al. 1994 [10], Israel</td>
<td>Prospective, uncontrolled</td>
<td>8/10</td>
<td>Perineal</td>
<td>2.5 ATA 100% oxygen; 90 min sessions; 6 times per week; 20 total treatments; HBOT could be stopped for rest of 40 sessions</td>
<td>none</td>
<td>10 patients with Crohn's disease refractory to standard medical treatments; improvement observed in 8 of 10 patients, 6 patients and complete healing</td>
</tr>
<tr>
<td>Nakan et al. 1990 [46], USA</td>
<td>Late report</td>
<td>1/1</td>
<td>Perineal</td>
<td>2.4 ATA 100% oxygen; 90 min session; not total of 82 sessions</td>
<td>none</td>
<td>Patient had severe refractory Crohn's disease (failed sulfasalazine and corticosteroids), complete healing with HBOT; no recurrence in 24 months after HBOT</td>
</tr>
<tr>
<td>Sapid et al. 2008 [47], Turkey</td>
<td>Prospective, uncontrolled Crohn's disease</td>
<td>1/4</td>
<td>Perineal</td>
<td>2.4 ATA 90 min session; 1 treatment per day</td>
<td>None</td>
<td>Strong improvement (improvement through vasoconstriction of brachial artery; clinical outcomes of HBOT on GI abnormalities in 2 patients with Crohn's disease not reported</td>
</tr>
<tr>
<td>Sipahi et al. 1996 [48], Brazil</td>
<td>Case report</td>
<td>1/1</td>
<td>Perineal</td>
<td>2.4 ATA; 90 min sessions; 7 times per week (1st 2 weeks) then 3 times per week; 43 total sessions over 3 months</td>
<td>NR</td>
<td>Complete healing of perianal Crohn's disease with HBOT and antibiotics</td>
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</tbody>
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