



Med Gas Res. 2012; 2: 6.

PMCID: PMC3328239

Published online 2012 Mar 15. doi: [10.1186/2045-9912-2-6](https://doi.org/10.1186/2045-9912-2-6)

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

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Received 2012 Jan 21; Accepted 2012 Mar 15.

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Abstract

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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

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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

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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", "Crohn's", "esophagitis", "gastritis", "duodenitis", "jejunitis", "ileitis", and "proctitis." Figure 1 demonstrates the flow chart of publications identified by the literature search.

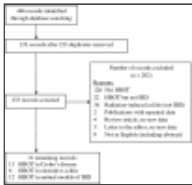


Figure 1
Flow diagram of studies.

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

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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-mercaptopurine, 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 contained patients from previous studies but reported new data on these patients [40,49]. One study reported the effects of HBOT on flow-mediated vasodilation of the brachial artery in 2 patients with Crohn's disease, but did not report the clinical outcomes of HBOT on gastrointestinal inflammation in these patients [47]. The remaining 9 studies [10,11,39,41,43-46,48] totaled 40 unique patients with Crohn's disease who were treated with HBOT ranging from 2.0 to 2.8 ATA. Of these 40 patients, 31 (78%) had clinical improvements in Crohn's disease with HBOT. One study reported a significant decrease in proinflammatory cytokines (IL-1, IL-6 and TNF-α) after HBOT in 7 patients with Crohn's disease [49].

Table 1 Studies of HBOT in Crohn's disease									
Study	Year	Type of study	Number of patients	Location of treatment	HBOT parameters	Results	Ref.	Year	Ref.
10	1990	Case report	1	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[10]	1990	[10]
11	1990	Case report	1	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[11]	1990	[11]
39	1990	Case report	1	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[39]	1990	[39]
40	1990	Case report	1	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[40]	1990	[40]
41	1990	Case report	1	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[41]	1990	[41]
42	1990	Case report	6	Dead Sea, Israel	1.05 ATA, 3 weeks	Improvement in Crohn's disease	[42]	1990	[42]
43	1990	Case report	1	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[43]	1990	[43]
44	1990	Case report	1	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[44]	1990	[44]
45	1990	Case report	1	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[45]	1990	[45]
46	1990	Case report	1	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[46]	1990	[46]
47	1990	Case report	2	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[47]	1990	[47]
48	1990	Case report	1	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[48]	1990	[48]
49	1990	Case report	1	Paris, France	2.0 ATA, 90 min	Improvement in Crohn's disease	[49]	1990	[49]

Table 1
Studies of HBOT in Crohn's disease

Studies on ulcerative colitis

Table 2 outlines the 6 studies [12,50-54] meeting inclusion criteria that reported the use of HBOT in ulcerative colitis. In each study, the patients had severe ulcerative colitis that was refractory to standard medical treatments, including, in some cases, corticosteroids, 6-mercaptopurine, mesalamine, tetracycline, 5-amino salicylic acid, and azathioprine. One case series [50] reported two patients with ulcerative colitis who improved with HBOT; one of

these patients had previously been reported [52]. One study from Bulgaria was not published in English, except for the abstract which reported that 34 patients with chronic ulcerohemorrhagic colitis had improvements with HBOT [53]; however, since only the abstract was written in English, the strengths and weaknesses of this study could not be adequately assessed. The remaining 5 studies [12,50-52,54] totaled 5 unique patients with all 5 reported as having improvements in ulcerative colitis with HBOT; each patient was treated at 2.0 ATA. One study reported a decrease in the IL-6 concentration with HBOT [54].

Table 2

Studies of HBOT in ulcerative colitis

Adverse events in Crohn's disease and ulcerative colitis

Of the 13 studies in Crohn's disease, 10 did not report if there were any adverse events [11,40,42-49]. One study reported that one patient had a bilateral ear drum perforation and another had psychological intolerance; both patients had to stop HBOT after a few sessions [41]. It should be noted that ear drum perforation and psychological intolerance are related to changes in pressure and confinement and not side effects of the oxygen being administered. Another study reported blurred vision in one patient which resolved spontaneously [39]. The final study in Crohn's disease specifically reported that there were no adverse events [10]. Of the 6 studies in ulcerative colitis, 3 studies did not report if there were any adverse events [12,51,53] while 3 studies specifically reported that there were no adverse events [50,52,54].

Studies of animal models of IBD

Table 3 outlines the 12 studies [55-66] meeting inclusion criteria that reported the use of HBOT in experimentally-induced colitis in an animal model of IBD. All 12 studies used rats as the animal model. One study was published only in abstract form [62] and another study was not published in English except for the abstract [65]. Most studies were published in Turkey except for two studies published in the United States [63,66] and one in Israel [64]. Several studies reported that HBOT reduced markers of inflammation, including TNF-alpha [61,63,66], IL-1 β [63,66] and neopterin levels [56]. HBOT also decreased edema or colonic tissue weight in 4 studies [56,57,62,64]. One study reported HBOT was equivalent in anti-inflammatory effect to dexamethasone [57]. Myeloperoxidase activity (an index of the accumulation of neutrophils) was reduced after HBOT in 5 studies [55,57,63,64,66]. Some studies reported that HBOT lowered markers of oxidative stress, including malondialdehyde [56,60,61] and plasma carbonyl content [55,61], except for one study that reported HBOT increased protein carbonyl content [65]. Two studies reported HBOT significantly increased glutathione peroxidase and superoxide dismutase levels [60,61]. HBOT also decreased nitric oxide [58,61,63] and nitric oxide synthase levels [63,64,66]. Finally, in one study, HBOT decreased prostaglandin E₂ levels [64]. Nine studies used histopathology scores to document changes with HBOT [55-61,64,65] and 8 reported microscopic improvements [56-61,64,65].

Table 3

Studies of HBOT in animal models of experimentally-induced colitis

Discussion

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Crohn's disease and ulcerative colitis are forms of IBD which have a limited repertoire of treatment options. Management consists of maintaining clinical remission. In the reviewed studies, HBOT was associated with improvements in most treated patients. Of note, all of the patients in these studies had IBD that was refractory to standard medical treatments and HBOT was essentially used as a treatment of last resort. Adverse events were

minimal in most studies. Several animal studies reported that HBOT decreased inflammation and oxidative stress markers and led to improvements in IBD on both a microscopic and macroscopic level.

Effects of HBOT on inflammation and immune dysregulation in IBD

IBD is characterized by inflammation, ulcerations and the accumulation of neutrophils. Many of the reviewed animal models replicated IBD by inducing colitis which was accompanied by intestinal edema, ulcerations, accumulation of neutrophils, increased nitric oxide levels and elevated cytokines. Therefore, these animal models appeared effective at reproducing the pathophysiology of IBD.

HBOT has been shown to possess potent anti-inflammatory properties in both animal [55,67,68] and human studies [10,11,20,46,69] and has been reported to decrease the production of pro-inflammatory cytokines (such as TNF-alpha, interferon-gamma, IL-1 and IL-6) in both animal [66,70] and human studies [20,49] as well as increase IL-10 levels [71]. Several of the reviewed studies (including human studies and animal models) reported a decrease in inflammation as measured by reduced tissue edema and histopathological changes, as well as a decrease in TNF-alpha, IL-1 and IL-6 with HBOT [49,54,61,63,66]. Some of these effects may have been mediated, to some degree, by the activity of stem cells [72]. Stem cells have been shown to migrate to the sites of inflammation and damage [73]. Several studies have reported that HBOT can stimulate the growth and differentiation of stem cells [74-78] as well as mobilize stem cells into the circulation from bone marrow [79,80]. A number of studies have reported improvements using stem cells in some patients with Crohn's disease [81-86] or ulcerative colitis [84]. Interestingly, some animal studies report that the use of HBOT combined with stem cells was more effective than stem cells alone [87-90]. Therefore, HBOT may help lower inflammation in patients with IBD through the increased mobilization of stem cells.

Animal models of IBD demonstrate that the GI mucosa develops hypoxia [91]. Hypoxia has been reported to increase oxidative stress and inhibit mitochondrial function [92] as well as increase inflammation [93]. Chronic inflammation can lead to tissue edema and impaired oxygen extraction from the blood into tissue [94] and a vicious cycle between hypoxia and inflammation can therefore ensue [95]. Hypoxia also causes an increase in hypoxia-inducible transcription factor (HIF) which, in turn, can initiate an inflammatory cascade [96,97]. In fact, HIF is essential for inflammation mediated by myeloid cells [98] and rats null for HIF demonstrate almost complete inhibition of the inflammatory response [99]. Furthermore, intestinal biopsies from patients with IBD show elevated levels of HIF in the mucosa [100]. Hypoxia and increased levels of HIF can then activate nuclear factor κ B (NF- κ B) which subsequently stimulates the production of TNF-alpha [101]. HBOT has been shown to inhibit the expression of HIF and its target genes [102]. Therefore, another method whereby HBOT may lower inflammation in patients with IBD is by the relief of hypoxia and the inhibition of HIF expression [95]. Interestingly, decreased blood flow to the rectum has been reported in some individuals with ulcerative colitis [8]. A reduction in tissue edema with the use of HBOT might lead to improved blood supply and relief of hypoxia. Therefore, HBOT may also ameliorate hypoxia and inflammation in individuals with IBD by reducing tissue edema.

Finally, the inflammation found in IBD could be secondary to an infectious agent. Since some investigators have reported that *Mycobacterium avium* subspecies paratuberculosis may play a role in IBD [7], it is possible the HBOT may be beneficial as it has been reported to kill *Mycobacterium* species [103,104]. Additional studies investigating the effects of HBOT on inflammation and biomarkers of inflammation in individuals with IBD are warranted.

Effects of HBOT on oxidative stress in IBD

Some studies have reported evidence of oxidative stress and mitochondrial dysfunction in individuals with IBD. Several of the animal models of IBD reported a reduction in oxidative stress markers with HBOT. It should be noted that, theoretically, HBOT might increase oxidative stress through the augmented production of reactive

oxygen species (ROS) from the high concentration of oxygen [105]. This may occur because increased oxygen delivery to mitochondria can increase ROS production. However, HBOT has also been shown to upregulate the production of antioxidant enzymes such as superoxide dismutase [106,107], glutathione peroxidase [60], catalase [108], paraoxonase [109] and heme-oxygenase 1 [110,111]. This increase in antioxidant enzyme levels has been termed "conditioning" and can protect against damage caused by ROS [95,112]. Two animal models of IBD reported a significant increase in glutathione peroxidase and superoxide dismutase levels with HBOT [60,61], suggesting that the increased production of antioxidant enzymes may have limited or lowered oxidative stress in these studies. Although none of the reviewed studies measured changes in mitochondrial function with HBOT, it is possible that HBOT may have led to some improvements by augmenting mitochondrial function as reported in previous studies [113-116]. Further studies examining the effects of HBOT on oxidative stress and mitochondrial dysfunction in individuals with IBD are needed.

Effects of HBOT on IBD in human studies

The total number of identified publications utilizing HBOT in Crohn's disease was about twice the number of studies in ulcerative colitis. In these studies, the number of patients treated in both diseases was similar, although one study in ulcerative colitis reported improvements in 34 patients, but this finding was only reported in an English abstract, and therefore the strengths and weaknesses of this study could not be adequately assessed [53]. The remaining 5 studies in ulcerative colitis only totaled 5 patients. Therefore, the evidence in the reviewed studies for a positive effect of HBOT is stronger for Crohn's disease than for ulcerative colitis.

In the studies of Crohn's disease, 78% of treated patients had an improvement with HBOT at a pressure ranging from 2.0 to 2.8 ATA. In the studies of ulcerative colitis, all treated patients showed improvements with a pressure delivered at 2.0 ATA. These studies suggest that a higher pressure may be needed to achieve these improvements. However, because none of these studies utilized a lower pressure of HBOT, it is not known if a lower pressure or oxygen level would be beneficial in IBD. However, some investigators have reported improvements in GI function in some children with autism using HBOT at 1.3 to 1.5 ATA [117,118]. Furthermore, previous studies have reported improvements in certain neurological conditions using hyperbaric treatment at lower pressures and/or oxygen levels [119-122]. Additional studies using HBOT at varying oxygen concentrations and atmospheric pressures would be helpful in determining optimal treatment protocols.

It is especially noteworthy that all of the studies on Crohn's disease and ulcerative colitis used HBOT in patients who were refractory to multiple medical treatments, including, in some cases, corticosteroids, 6-mercaptopurine, mesalamine, tetracycline, 5-amino salicylic acid, azathioprine, sulfasalazine, metronidazole, and an elemental diet. It is possible that earlier treatment with HBOT in individuals with IBD before severe symptoms develop would be even more effective in ameliorating the condition. Additional studies examining the clinical effects of HBOT in individuals with IBD would be helpful in assessing this possibility.

Limitations

Many of the reviewed studies suffered from limitations, including the lack of a control group, the open-label nature and the small number of participants. Some of the studies were retrospective while only a few were prospective [10,41-43,47,49]. Most of the reviewed studies did not report if HBOT was supplied in a monoplace or multiplace chamber, and whether or not masks or hood systems were used, and therefore the ability to determine the effects of different types of chambers or oxygen delivery systems in these studies could not be adequately assessed. Most studies did not specifically report if there were any adverse events. Presumably, if there had been any adverse events, the investigators would have reported them. Therefore, the adverse events in these studies were most likely minimal, but since most studies did not report this, a full assessment cannot be performed. Some of the studies may have been limited by referral bias; for example, none of the studies were population-based which could have reduced potential referral bias. Another limitation of the studies may have

been publication bias where only cases that had improvements with HBOT were published, and cases of IBD that were treated with HBOT that did not improve may not have been published. However, it should be noted that for a new treatment to be recognized, it is common for case reports to first be published to introduce and confirm a new treatment before sufficient interest is generated to commit resources to completing larger high-quality, stronger studies. Since most reviewed studies had limitations, larger studies examining the effects of HBOT in individuals with IBD are warranted.

Conclusions

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HBOT ameliorated symptoms of IBD in both human studies and animal models. HBOT also lowered pro-inflammatory cytokine concentrations and lowered biomarkers of inflammation and oxidative stress. Adverse events were minimal. Many 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. Additional studies are warranted to investigate both the effects of HBOT on biomarkers of oxidative stress and inflammation as well as clinical outcomes in individuals with IBD.

Abbreviations

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ATA: Atmosphere absolute; GI: Gastrointestinal; HBOT: Hyperbaric oxygen treatment; IBD: Inflammatory bowel disease; NO: Nitric oxide.

Competing interests

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The author treats individuals with HBOT in his clinical practice and derives revenue from this. He has previously received research funding from the International Hyperbarics Association (IHA) for two studies of hyperbaric treatment in children with autism [120,121] and is a medical advisor (unpaid) for IHA.

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