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Hyperbaric Oxygen Therapy for Perineal Crohn's Disease

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Perineal lesions are a frequent and troublesome complication of Crohn's disease. Although there are various surgical and medical therapeutic regimens available to treat these lesions, all have significant associated morbidity, mortality, and toxicity. Recently, the beneficial effects of hyperbaric oxygen therapy (HBOT) have been described in patients with severe or refractory perineal disease, but the role of HBOT in larger groups or less severely affected patients has not yet been studied, nor has the minimum number of treatments required for initial or complete healing of perineal disease in this population been described. This article reviews the known and theoretical tissue effects of HBOT and discusses its potential role in treating patients with perineal Crohn's disease. (Am J Gastroenterol 1999;94:318–321. © 1999 by Am. Coll. of Gastroenterology)

INTRODUCTION

Perineal involvement can be a significant cause of morbidity in patients with Crohn's disease (1). Medications such as 6-mercaptopurine/azathioprine or metronidazole may require months to take effect. Others, including metronidazole, methotrexate, and cyclosporine, have dose-limiting toxicity and significant side effects (2–6). Surgery may temporarily alleviate abscesses and fistulae but does not necessarily improve the underlying perineal disease. Several reports on the use of HBOT in patients with severe or refractory perineal Crohn's disease have shown promising results, although whether this therapy might benefit those with less severe perineal disease is unclear (7–11).

HISTORY OF HYPERBARIC THERAPY

A physician named Henshaw first attempted to treat patients in a chamber with altered pressure about 300 years ago (12). Paul Bert, in the late 1800s, studied the effects of altered pressure on animals and humans and described his work in a fascinating tome (13). About that time, the first therapeutic compression chamber was built in the United States and located in Rochester, New York. Much of the impetus for the development of the hyperbaric chamber came from the need to treat decompression sickness (caisson disease) accompanying construction projects such as the Brooklyn Bridge, which took workers 78 feet below sea level. During and after World War II, the US Navy and Air Force recognized the need for HBOT, and they established a hyperbaric medicine program about 1960. Initial widespread enthusiasm for HBOT led to its inappropriate use, and the field fell into disrepute. More recent and reputable studies have demonstrated its role in treating specific illnesses.

INDICATIONS AND CONTRAINDICATIONS OF HBO THERAPY

Hyperbaric oxygen involves the intermittent inhalation of 100% oxygen at a pressure $>$ 1 atmosphere absolute (ata) (14). Although used most commonly for decompression sickness or carbon monoxide poisoning, HBOT is indicated for *Clostridia*-related gangrene, necrotizing soft tissue infection, radiation necrosis, refractory osteomyelitis, and chronic wounds (14). HBOT has been used with success in pyoderma gangrenosum, an extraintestinal manifestation of inflammatory bowel disease (15, 16). Theoretically, HBO enhances the healing of chronic wounds by its ability to optimize fibroblast proliferation and white blood cell killing, otherwise limited during periods of hypoxia, and by its stimulation of angioneogenesis (see later here).

RATIONALE FOR USE IN CROHN'S DISEASE

The rationale for using HBOT in patients with perineal disease comes from several observations regarding the pathogenesis of Crohn's disease. Ubiquitous anaerobic bacteria and their cell wall components are believed to be involved in the perpetuation of Crohn's disease, the induction of extraintestinal manifestations of IBD, the pathogenesis of pouchitis, and the development and perpetuation of perineal disease (17). HBOT, by increasing the oxygen tension in inflamed or poorly perfused tissue, enhances the oxygen burst necessary for phagocytic killing of organisms and facilitates tissue repair by augmenting fibroblast collagen synthesis. Under conditions of 100% inspired oxygen at 3 atmospheres, the plasma oxygen content increases almost 20-fold, from 0.32 to 6.8 vol% (18). Transcutaneous oxygen measurement of perineal wounds in a patient with Crohn's disease revealed an oxygen tension of 18 mm Hg with a chest control value of 66 mm Hg. Under conditions of

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HBOT with the patient receiving 100% oxygen at 2.4 atmospheres, wound site oxygen tension increased to 636 mm Hg; healing of the lesions ensued (7).

Inflammatory bowel diseases are believed to result from inappropriately prolonged and intense inflammatory responses to unknown stimuli or agents. Inflammatory cell recruitment in IBD involves several components, including enhanced binding of leukocytes to mucosal microvascular endothelial cells and leukocyte influx into the mucosa (19). After adhering to endothelial cells, neutrophils enter the intestinal mucosa by migrating through tight junctions. The adhesion process begins with the interactions between selectins and integrins, both present on neutrophils and endothelial cells. Additional bonding occurs between selectins and their ligands, and between integrins on neutrophils and ICAM-1 (intercellular adhesion molecule) and VCAM-1 (vascular cell adhesion molecule), members of the immunoglobulin (Ig) superfamily, present on endothelial cells (20). Different studies have found varying levels of soluble ICAM-1 and VCAM-1 in patients with Crohn's disease (20). Further activation of neutrophils occurs *via* interaction with ligands such as FMLP (N-formyl-methionyl-leucine-phenylaline), a peptide produced by intestinal bacteria and present in the colonic lumen. Although what initiates this inflammatory process is unknown, HBOT has been shown in rats to inhibit leukocyte β2 integrin-dependent adherence and the neutrophil response to FMLP (21). A more recent study on human neutrophils has confirmed that HBOT inhibits the function of human neutrophil β2-integrins by a process linked to impaired synthesis of cGMP (22). FMLP has the potent ability to incite inflammation and activate soluble, inflammatory mediators. It is also a potent activator of neutrophils, eliciting chemotaxis and lysosomal enzyme production. Patients with active Crohn's disease have circulating neutrophils with increased numbers of FMLP receptors (23).

Levels of cytokines such as IL-1 and TNF-α, which are elevated in patients with perineal Crohn's disease and can upregulate expression of selectins, decrease to normal levels during HBOT (18, 24). The effects of HBOT on lymphocytes are not as well defined, but one study of HBOT in normal and autoimmune mice showed that different subpopulations of lymphocytes in the thymus and spleen have varied sensitivities to HBOT (25).

COMPLICATIONS AND SIDE EFFECTS

The complications of HBO are related to the changes in barometric pressure and oxygen toxicity. Patients can relieve the mild inner ear discomfort that may occur by using certain maneuvers (*e.g.*, swallowing or gently blowing out against compressed nostrils). The most common complication is middle ear or sinus trauma (14). Pneumothorax and air embolism are rare complications, occurring in patients with underlying lung disease (14). Oxygen toxicity does not occur in the HBOT protocols used to treat IBD, whereas maturation of cataracts has been reported after more than 150 treatments (26).

RESULTS OF HBO THERAPY FOR PERINEAL DISEASE

Brady *et al*. in 1989 were the first to report using HBOT for severe perineal Crohn's disease (7). Their patient's lesions, which failed to heal after multiple surgical interventions and treatment with antibiotics, immunomodulators, and 5-ASA agents, responded completely to HBOT. Since that initial report, 21 other patients have been described who received HBOT for perineal Crohn's disease (Table 1); all had either severe or refractory perineal lesions. In two studies, response rates were 60% and 100%, if all patients who were enrolled were included (10, 11). Of all 22 patients described in the literature, 16 (73%) had a complete response to HBOT, two (9%) a partial response, and four (18%) no response (this last includes two drop-outs) (7, 9–11). Of interest is the fact that several patients with Crohn's disease who were vacationing at the Dead Sea—an environment of increased oxygen tension—had improvement in perineal and ileocolic disease (27).

In the report by Colombel *et al*., two patients discontinued treatment after only a few sessions. One patient suffered bilateral tympanic membrane perforation, and the other could not tolerate treatment for psychological reasons (11). The patient reported by Brady *et al*. complained of blurred vision, which resolved after treatments were completed (7). Lavy *et al*. did not report any side effects in their patients (10). In three of the four reports that included surgical histories, all of the patients had required surgical interventions before HBOT.

CONCLUSIONS

Although HBOT is effective in patients with severe perineal Crohn's disease, its effects on less severe perineal disease (*i.e.*, those cases with "nuisance," quiescent, or incompletely healed fistulae) are unknown. HBOT might serve as a steroid-sparing agent or act as a bridge until medications such as azathioprine or 6-MP have had time to take effect. The minimal number of treatments necessary to see an improvement or complete healing is unknown, as is the long term outcome of this treatment. It is unclear what the dropout rate for treatment would be if less severely affected patients were treated. The considerable time commitment is a drawback that could be overcome if studies were to show that less frequent treatment is as effective as more intensive regimens.

FUTURE IMPLICATIONS

The role of hyperbaric oxygen therapy in perineal Crohn's disease remains unclear. Further studies in patients with this chronic and disabling disease would determine whether broader selection criteria are appropriate in identi-

TABLE 1
Summary of Previous HBO Therapy Reports

Study	Patient	Surgical Rx	Disease Location	Medications	Perineal Lesions	HBO Rx	Oxygen	Response	Side Effects	Note
Brady	1	diversion, proctosigmoidectomy	colon	ASA, metronidazole, abx, steroids, 6-MP	stricture, abscesses	2.4 atm/2 h/67 sessions	100% FM	CR	blurry vision (resolved)	
Nelson	1	colostomy, proctocolectomy, ileostomy	colon	ASA, steroids, metronidazole, azathioprine	fistula, abscess	2.0 atm/2 h/64 sessions	?	CR	none reported	
Colombel	1	local	?	5-ASA azathioprine, zinc	fissure, fistula	2.5 atm/2 h/36 sessions	100% FM	PR/NR	?	
	2	ileocolectomy	?	5-ASA azathioprine, zinc	fissure, fistula	2.5 atm/2 h/30 sessions	100% FM	NR	?	
	3	local	?	metronidazole	fistula	2.5 atm/2 h/30 sessions	100% FM	NR	?	
	4	protocolectomy	?	metronidazole azathioprine	wound	2.5 atm/2 h/40 sessions	100% FM	PR/CR	?	CR s/p 55 sessions
	5	local	?	metronidazole	ulcer, fistula	2.5 atm/2 h/36 sessions	100% FM	CR	?	
	6	ileal resection	?	metronidazole azathioprine	ulcer, fistula	2.5 atm/2 h/40 sessions	100% FM	CR	?	
	7	hemicolectomy, colostomy	?	5-ASA	fissure, fistula	2.5 atm/2 h/33 sessions	100% FM	CR	?	
	8	local	?	5-ASA	fissure, fistula	2.5 atm/2 h/31 sessions	100% FM	PR/CR	?	
	9	hemicolectomy, colostomy	?	metronidazole, azathioprine, salazopyrine	ulcer, stricture	Did not complete	100% FM	NR	barotrauma	
	10	local	?	metronidazole, 5-ASA	fissure, fistula	Did not complete	100% FM	NR	claustrophobia ?	
Lavy	1	?	colon	azulfidine	fistula	2.5 atm/1.5 h/20	100% FM	CR	none	
	2	?	ileum	5-ASA	infiltration	2.5 atm/1.5 h/20	100% FM	CR	none	
	3	?	rectum	azulfidine	fistulae, stricture	2.5 atm/1.5 h/20	100% FM	PR/CR	none	CR s/p 60
	4	none	colon	5-ASA	fistula	2.5 atm/1.5 h/20	100% FM	PR/CR	none	CR s/p 40
	5	?	colon	azulfidine	fistula	2.5 atm/1.5 h/20	100% FM	PR/CR	none	CR s/p 40
	6	?	ileum, colon	5-ASA	fistula	2.5 atm/1.5 h/20	100% FM	PR/PR	none	PR s/p 40
	7	?	ileum, colon	azulfidine	fistula	2.5 atm/1.5 h/20	100% FM	CR	none	
	8	?	colon	azulfidine	fistulae	2.5 atm/1.5 h/20	100% FM	PR/CR	none	CR s/p 60
	9	?	ileum	5-ASA	fistulae	2.5 atm/1.5 h/20	100% FM	PR/PR	none	PR s/p 60
	10	none	none	none	fistulae	2.5 atm/1.5 h/20	100% FM	PR/CR	none	CR s/p 60
Total #	22						16 CR	2 PR	4 NR	

CR: complete response; PR: partial response; NR: no response; abx: antibiotics.

fying patients with perineal lesions who might benefit from HBOT. Basic laboratory investigation would pave the way for expanded clinical insights. The effects of HBOT on neutrophil or lymphocyte behavior and on levels of IL-1, IL-6, and TNF-α are just a few of the studies waiting to be done.

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