ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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The Potential Role of Hyperbaric Oxygen Therapy in Patients With Inflammatory Bowel Disease

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G&H Why has hyperbaric oxygen therapy been considered for the treatment of patients with inflammatory bowel disease?

PD Inflammatory bowel disease (IBD), which encompasses both Crohn's disease and ulcerative colitis, is a multifactorial autoimmune disorder of the gastrointestinal (GI) tract. One of the core components of IBD is hypoxia, or low oxygen tension, in the GI tract. Normally, the GI tract does not have high levels of oxygen tension at the surface of the lining of the interior, and human bodies are adept at dealing with fluctuations in oxygen. However, when there are breaks in the lining, like what happens in IBD, and there is exposure to bacteria, immune cells infiltrate and consume whatever oxygen is there very rapidly. This causes extreme depletion of oxygen and relative hypoxia that then promotes progression of inflammation by allowing bad bacteria or anaerobes to persist as well as for the immune cells to persist and continue to contribute to the inflammation. It has been known for a long time that hypoxia is a critical regulator of inflammation in IBD. Researchers have just never found a good way to target hypoxia in the past because it is such a central physiologic process to the human body that targeting the independent pathways that are involved is difficult.

Hyperbaric oxygen therapy is a technology that has been around for a long time that offers an opportunity to hyperoxygenate tissue at a level that would not be achievable in any other manner. In this treatment approach, the patient enters a closed see-through chamber in which the air is changed out for 100% oxygen. The patient is pressurized in the chamber, similar to deep sea diving, where the pressure from the chamber drives oxygen to dissociate from an individual's blood into their tissues in a manner that would not otherwise be possible if they were just breathing a large amount of oxygen at normal pressure. That pressure, combined with the breathing of 100% oxygen, allows for hyperoxygenation of tissues that normally have low oxygen tension. That is why this treatment has been successful for chronic wounds such as diabetic foot wounds and other scenarios where low oxygen or absence of oxygen is critical, such as limb ischemia. In applying some of those concepts in our understanding of IBD, there has been growing interest in seeing whether these chambers can be used to target a central process of IBD to treat this disease.

G&H What research has been conducted thus far on this therapeutic approach in patients with IBD?

PD Going back decades, there have been case reports on the use of hyperbaric oxygen therapy in both ulcerative colitis and Crohn's disease. There has also been slow growth in the use of this approach in small case series or cohort studies. In terms of high-quality evidence that has been generated for hyperbaric oxygen therapy in the setting of IBD, there are 2 scenarios where this approach has been used very successfully. One is in patients who are hospitalized with severe ulcerative colitis flares. In 2 clinical trials, our group has demonstrated that using this treatment in patients who are hospitalized with severe ulcerative colitis flares and are at risk for requiring surgery or rescue therapy in the hospital can achieve very rapid

reductions in inflammation, improvements in bleeding, as well as improvements in inflammation of the colon as measured by direct visualization of the lining using lower endoscopy. These benefits allow patients to leave the hospital and start other medications for maintenance. Additionally, our group and several other groups have been looking at hyperbaric oxygen therapy in Crohn's disease, specifically trying to heal complicated fistulas or perianal wounds. Those appear to be similar to chronic abscesses or wounds where the properties of hyperbaric oxygen therapy can be used to relieve hypoxia as well as help with blood vessel growth and wound healing to achieve healing of perianal fistulas. That has been demonstrated in several prospective clinical studies to date. A number of institutions are now starting to use hyperbaric oxygen therapy in clinical practice in these 2 scenarios.

G&H Has hyperbaric oxygen therapy been studied in any other IBD subgroups?

PD There are case reports on the use of hyperbaric oxygen therapy in patients with mild, moderate, or severe ulcerative colitis in the outpatient setting, which appears to be quite promising with response rates of 70% to 80%. There are not as much data for studying hyperbaric oxygen therapy in Crohn's disease patients who do not have fistulas (ie, luminal Crohn's disease). Some data are starting to be generated and some clinical observations are becoming available for the use of this therapeutic approach in Crohn's disease patients who have undergone surgeries and have anastomotic ulcers. The thought is that low blood volume, ischemia, and hypoxia are contributing to the persistence of those ulcers and the need for those patients to receive repeat transfusions and other interventions.

G&H Within the aforementioned subgroups, which patients appear to be ideal candidates for this approach and which should avoid it?

PD One of the advantages of hyperbaric oxygen therapy is that it has very few contraindications, meaning it is generally safe and well-tolerated by a vast majority of patients. In that capacity, there are very few people who are not good candidates for hyperbaric oxygen therapy. There are some comorbid medical conditions that may prevent the use of this treatment, such as a history of seizures or severe medical complications that might preclude the ability to go into the chamber, but it is often rare for patients to be excluded or not to be good candidates for this treatment. Therefore, I think it is a reasonable option to attempt in most ulcerative colitis patients hospitalized with severe ulcerative colitis flares. For Crohn's disease patients, I think this treatment is particularly reasonable to attempt in those who have perianal wounds or chronic nonhealing fistulas.

G&H Are there any safety concerns or potential risks with the use of hyperbaric oxygen therapy?

PD It is an extremely safe and well-tolerated intervention. When dealing with very high pressures, there is a very rare risk of seizures or oxygen toxicity. However, those are not typically seen at the pressures often used in routine practice for IBD. As with any scenarios where a patient has to go into a chamber, there may be some anxiety or claustrophobia. The chamber is relatively large, but patients who cannot tolerate magnetic resonance imaging or computed tomography scans because of claustrophobia or anxiety likely are not good candidates for hyperbaric oxygen therapy because they may experience similar symptoms.

Chronic use of this treatment can have some long-term risks related to cataracts or vision changes because of the high amount of oxygen exposure. It is therefore recommended that patients do not undergo more than 30 sessions in total. This therapy should not be used repeatedly over time; it should ideally be used once or twice to try to get out of a flare to help healing and then the patient should find a medication that allows them to maintain that healing.

G&H What appears to be the optimal protocol in terms of the number of sessions and duration?

PD For ulcerative colitis, hyperbaric oxygen therapy should be administered for a minimum of 5 consecutive days at 1 session per day. Ideally, there would be 10 sessions for 2 weeks, with 1 session per day for 5-day blocks. The pressure should be around 2.4 to 2.5 atmospheres, and 100% oxygen should be used. For Crohn's disease patients with perianal fistulas, treatment typically lasts 4 to 6 weeks with 1 session per day at 5 days a week. Thus, the number of sessions would be higher, at 20 to 30. However, there would be a similar pressure of 2.4 to 2.5 atmospheres with 100% oxygen. For both ulcerative colitis and Crohn's disease, each session lasts approximately 90 to 120 minutes.

G&H With this treatment approach, what follow-up care is needed for IBD patients?

PD Hyperbaric medicine providers will use their usual follow-up care to make sure patients do not experience

middle ear pressure changes or damage to their tympanic membrane. There is an approximately 1% risk that the patient could have trouble equalizing the pressure, like when going on a flight or deep-sea diving. The provider needs to check that the patient's middle ear pressure equalizes. The rest of follow-up is routine IBD-specific care, such as monitoring symptoms and biomarkers like calprotectin to make sure the inflammation is improving and then undergoing follow-up imaging for perianal fistulas or colonoscopy or sigmoidoscopy to assess colon healing.

G&H Overall, what are the advantages and disadvantages of using hyperbaric oxygen therapy in patients with IBD?

PD The advantages are that it is readily available, safe, potentially highly effective for the aforementioned IBD subgroups, and can be added onto any therapy that patients are receiving. It does not require patients to deviate from what they would normally do for their standard of care. It can augment the response to that process.

As for disadvantages, one is that hyperbaric oxygen therapy is not approved by the US Food and Drug Administration for these indications. Because it is considered off-label use, reimbursement has been a challenge and is on a case-by-case basis. Out-of-pocket cost, however, should be relatively low because the treatment only requires a chamber with oxygen and a technician running it. Nevertheless, the cost can vary from location to location. Another disadvantage is that hyperbaric oxygen therapy can be time-consuming. Patients have to take out approximately 2 hours a day for 2 to 6 weeks for this treatment, which may not be practical on a regular basis.

G&H What has been the reaction to this treatment approach from patients and the medical community overall?

PD Patients love it. At least 1 patient a week wants to meet with me in the clinic to talk about it and understand it. It resonates very well for patients because it targets basic concepts and fundamental cores for treating inflammation with oxygen. Hyperbaric oxygen chambers are available routinely across the country and the world, so this approach involves established practices. The medical community likes the idea of using a treatment that is safe, noninvasive, and can be used alongside the medications patients are already using that suppress the immune system. Some people might mistakenly believe that hyperbaric oxygen therapy does not have any science behind its use, but researchers have generated and published on a lot of science that demonstrates how this treatment works to improve inflammation in IBD. Overall, this treatment has been well received, and now the focus should be on generating further evidence to help support its consistent use and reimbursement.

G&H What additional research is needed before hyperbaric oxygen therapy can be adopted further?

PD My colleagues and I are currently conducting a large clinical trial across 16 centers in the United States, funded by the National Institutes of Health, to determine the clinical utility and value of this treatment in hospitalized ulcerative colitis patients. If positive, this trial should cement the use of hyperbaric oxygen therapy in that population and allow for its expansion into the outpatient setting, as well as the studying of it in other scenarios. In Crohn's disease, a well-designed sham-controlled trial is needed to confirm its effectiveness for perianal fistulas. That is a gap that needs to be addressed.

Disclosures

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Suggested Reading

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