

Adjunctive Hyperbaric Oxygen Therapy promotes successful healing in patients with refractory Crohn's disease¹

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ABSTRACT

PURPOSE: To investigate the adjunctive effect of Hyperbaric Oxygen Therapy in a group of patients with refractory Crohn's disease.

METHODS: A total of 29 subjects with refractory Crohn's disease were submitted to daily sessions of Hyperbaric Oxygen Therapy, in a 2800 Sechrist Monoplace Hyperbaric Chamber (Sechrist, USA) pressurized to 2.4 ATA. Each session lasted 2 hours. The endpoint was closure of enterocutaneous fistulas and complete healing of Pyoderma Gangrenosum and perineal Crohn's disease.

RESULTS: A total of 829 HBOT sessions were performed and no complications were noted. Overall success rate was 76% (22 cases). Pyoderma Gangrenosum and enterocutaneous fistulas had the highest successful healing rates (100% and 91%, respectively). Perineal Crohn's disease healing rate was 65%.

CONCLUSION: Adjunctive Hyperbaric Oxygen Therapy promoted satisfactory healing in a group of patients with refractory Crohn's disease.

Key words: Hyperbaric Oxygenation. Crohn Disease. Cutaneous Fistula. Pyoderma Gangrenosum.

Introduction

Crohn's disease (CD) is a chronic inflammatory condition resulting from aberrant immune system activation. The disease primarily affects the gastrointestinal system but other organs may be involved¹.

Clinical manifestations are heterogeneous and may vary from mild cases (abdominal pain, changes in bowel habit and weight loss) to serious complications such as acute abdomen, perineal sepsis, fistulizing disease and colorectal cancer. The course of the disease is usually relapsing but some individuals may experience continuous inflammation².

Since CD cannot be cured, most treatment options aim the induction and maintenance of remission by controlling inflammation. Surgery is usually recommended for non-responsive or complicated cases³.

Some studies have shown benefits of hyperbaric oxygen therapy (HBOT) especially in the treatment of complex perineal wounds, pyoderma gangrenosum (PG) and fistulizing disease⁴⁻⁸. HBOT is a treatment modality that consists in 100% oxygen breathing in pressurized chambers. The improvement with HBOT is attributed to local events (such as neovascularization and reduced hypoxia, stem cell mobilization/differentiation and extracellular matrix formation) and systemic effects (decrease in proinflammatory cytokines and biomarkers of oxidative stress)⁹⁻¹¹.

The purpose of this study was to evaluate the adjunctive effect of HBOT in a group of patients with of pharmaco-refractory perineal Crohn's disease (PCD), enterocutaneous fistulas (ECF) and PG.

Methods

Patients

A prospective institutional review board-approved study was conducted at Clinics Hospital-University of São Paulo

(Ribeirão Preto, SP, Brazil). A total of 29 patients with pharmaco-refractory CD associated with ECF, PCD or PG were selected to HBOT, from 2008 to 2015. An informed written consent was provided in all cases. Hyperbaric sessions were performed at Hyperbaric Medicine Center-São Paulo Hospital (Ribeirão Preto, SP, Brazil) that keeps a prospective, database of all sessions.

Hyperbaric oxygen therapy

Daily HBOT sessions were performed in a 2800 Sechrist Monoplace Hyperbaric Chamber (Sechrist, USA) pressurized to 2.4 ATA and lasted 2 hours, each. The number of sessions was not constant and varied according to the clinical outcome of patients in order to obtain the best results. Basic care of chronic cutaneous lesions was maintained throughout the entire treatment and included cleaning and dressings, antibiotics and surgical debridement when needed. The result of HBOT was classified as satisfactory or unsatisfactory, when improvement could not be noted.

Results

The most common indication for HBOT was PCD (n=15 / 51.7%) followed by ECF (n=8 / 27.5%) and PG (n=3 / 10.3%). An association between ECF and PCD was noted in 1 (3.5%) case. Concomitant ECF and PG were found in 1 (3.5%) patient. One patient (3.5%) exhibited all three complications. Table 1 summarizes some of the patients and treatment characteristics.

The median number of sessions was 20 (range, 10-86). A total of 829 HBOT sessions were performed and no complications were noted. Overall success rate was 76% (22 cases). Figure 1 illustrates some cases before and after HBOT. PG and ECF had the highest successful healing rates (100% and 91%, respectively). PCD completely healed in 65% of the cases. The remaining patients had an unsatisfactory response and needed major surgery (intestinal diversion with proctectomy or abdominal-perineal amputation of the rectum).

TABLE 1 - Main characteristics of patients and treatment.

Patient	Sex	Age	Indication	Sessions	Side effects	Response
1	F	28	ECF	23	No	Satisfactory
2	F	65	ECF	11	No	Satisfactory
3	M	33	PCD	61	No	Unsatisfactory
4	M	60	PG	20	No	Satisfactory
5	M	50	PCD	37	No	Unsatisfactory
6	F	38	PCD	20	No	Unsatisfactory
7	M	20	PCD	39	No	Unsatisfactory
8	F	43	ECF	10	No	Satisfactory
9	F	34	PCD	10	No	Satisfactory
10	M	25	ECF	86	No	Satisfactory
11	F	25	PG	26	No	Satisfactory
12	F	31	ECF	26	No	Satisfactory
13	F	42	PG	20	No	Satisfactory
14	M	29	ECF/PD	20	No	Satisfactory
15	M	45	ECF	20	No	Satisfactory
16	M	20	PCD	20	No	Unsatisfactory
17	F	41	PCD	32	No	Satisfactory
18	F	41	PCD	20	No	Satisfactory
19	M	41	ECF/PG	40	No	Satisfactory
20	M	32	PCD	40	No	Satisfactory
21	F	52	PCD	20	No	Satisfactory
22	F	41	PCD	40	No	Satisfactory
23	M	35	ECF	20	No	Satisfactory
24	M	38	PCD	30	No	Satisfactory
25	F	42	PCD	18	No	Unsatisfactory
26	M	32	ECF	20	No	Unsatisfactory
27	F	49	ECF/PCD/PG	50	No	Satisfactory
28	M	11	PCD	20	No	Satisfactory
29	M	31	PCD	30	No	Satisfactory

ECF: enterocutaneous fistula, PCD: perineal Crohn's disease, PG: pyoderma gangrenosum

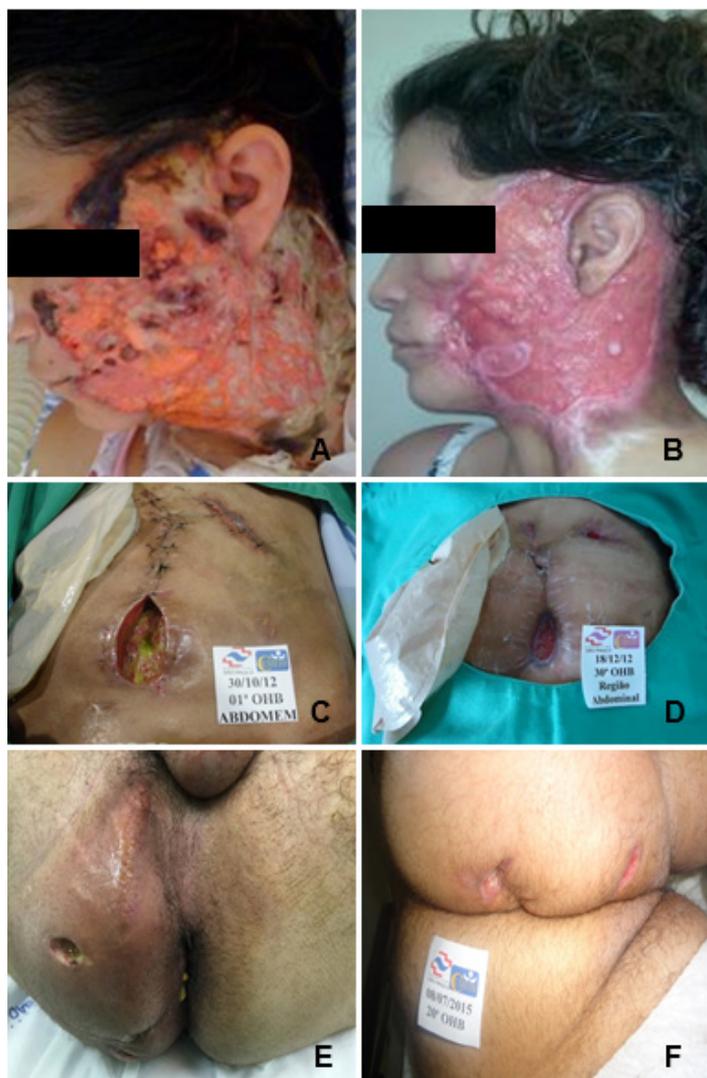


FIGURE 1 - Patients submitted to Hyperbaric Oxygen Therapy. First row: facial Pyoderma Gangrenosum before (A) and after 30 sessions (B). Second row: low-output enterocutaneous fistula before (C) and after 30 sessions (D) evidencing ongoing healing of the abdominal wound and complete fistula closure. Third row: Infected perineal Crohn's disease submitted to seton procedure and abscess drainage (E) evidencing reduction of edema and no infection after 30 sessions (F).

Discussion

The complete pathogenesis of CD is unclear. Animal models of colitis have shown that intestinal hypoxia may be observed as inflammation aggravates¹². This hypoxic microenvironment, in thus, is a potent stimulus to further inflammation and apoptosis via increases in hypoxia-inducible transcription factor (HIF) levels¹³. This state of perpetual inflammation can be halted by increases in tissue oxygenation¹⁴. Measurements of oxygen tension on perineal wounds may exhibit increases up to 35 times after HBOT¹⁵.

Perianal disease can be found in up to 35-45% of CD patients. Anorectal abscesses, fissures and fistulas are the most common findings¹⁶. Appropriate treatment involves the use of

symptomatic medication, local care (cleansing and sitz baths), antibiotic therapy and immunomodulators in some cases¹⁷⁻²¹. Surgery is usually recommended for resistant or complex perineal wounds. Care should be taken to avoid extensive damage since poor healing may be found, specially if severe proctitis is present²².

Reported response rate for perineal disease treated in regimens of hyperoxygenation range from 75-100%⁴⁻⁸. In the present study, complete healing of PCD was obtained in the majority of patients. Although minor surgical procedures were necessary to remove devitalized tissues and control infection, no intestinal diversion or proctectomy was necessary in the group that responded to HBOT.

The effects of HBOT in complex wounds include: decreased inflammation and tissue edema, mobilization of stem cells, neovascularization, fibroblasts growth and extracellular matrix formation²³⁻²⁶. Those changes in wound microenvironment are powerful stimuli towards healing and could explain some of the results found in CD patients with complex wounds. The same rationale could be used to explain the pain relief, systemic corticosteroids reduction and accelerated healing in PG patients²⁷.

The use of HBOT in enterocutaneous fistulas may be appropriate if output volume is low. Complicated Fistulas with higher debit, chronic course, labiate, with satellite collection and distal obstruction may have an initial conservative approach; yet, surgery is usually the definite treatment²⁸. In the present study, treatment of ECF with HBOT was considerate excellent; however, patients were evaluated immediately after the HBOT sessions and there is no long-term follow-up. Healing failure was found in only one patient with a chronic fistula of high output volume. This successful healing rate may be explained by the systemic antiinflammatory properties of HBOT¹².

The results of this research are encouraging since patients who were refractory to maximum medical treatment obtained high healing rates; however, the small number of patients, the short-term follow-up and the lack of a control group limit our conclusions. Part of the good results could be explained by the close monitoring of patients that included daily clinical evaluations, intensive wound care and optimization of medical therapy. A prospective controlled study could solve this problem; yet, it would be ethically questionable to create a control group and deny a possibility of treatment in patients with an aggressive condition and limited therapeutic options. This pattern of limitation is shared by most studies that deal with HBOT in severe/refractory CD. The authors believe that a randomized controlled trial with HBOT in CD patients in earlier stages of disease is necessary and will contribute to reduce biases.

Conclusion

A high healing rate was observed in a group of patients with complicated and refractory CD after HBOT. No complications were found during the procedure. The results suggest that HBOT may have an adjunctive role in CD complications. Further investigation is necessary to strengthen our findings.

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