Hyperbaric Oxygenation in Severe Perineal Crohn's Disease

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PURPOSE: Perineal involvement in Crohn's disease is a common and distressing condition, often refractory to medical or surgical treatments. Recent reports suggest the efficacy of hyperbaric oxygenation (HBO) in the healing of perineal lesions. We evaluated HBO in severe patients with perineal Crohn's disease. METHODS: Ten consecutive patients (8 women, 2 men; mean age, 30 years) were studied. There were four superficial fissures, four cavitating ulcers, six low or superficial fistulas, two high fistulas, and one irreversible anal stenosis. All patients had received one or more medical treatments without healing the perineal lesions, and all had had previous surgery for perineal lesions. RESULTS: Two patients discontinued HBO after a few sessions and did not complete treatment. Eight patients completed at least 30 HBO sessions and were evaluable. At the end of the procedure, six of eight patients treated were healed, three completely and three partially. All patients who healed completely received HBO as an additional treatment to local perineal surgery. CONCLUSION: HBO might be useful as a last resort treatment of chronic perineal Crohn's disease, resistant to other treatments or as a complement to surgery. [Key words: Crohn's disease; Perineal; Hyperbaric oxygenation]

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Perineal Crohn's disease (CD) is common, distressing, and frequently refractory to treatment.[1–4] Several reports suggest that metronidazole may be beneficial[5, 6] though controlled studies are lacking, and side effects such as sensitive neuropathy have limited its usefulness.[7] Most other conventional therapies (sulfasalazine and 5-aminosalicylate, steroids) are not effective. Total parenteral nutrition and immunosuppressive drugs may be beneficial, but relapse is common.[8–10] Current surgical procedures give good results in many patients, but eventually diverting ileostomy or colostomy with or without proctocolectomy remain mandatory in severe forms.[11–14]

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Pathogenesis of perineal CD is unclear, but local ischemia and secondary anaerobic infection are likely to play a role. In 1989, Brady *et al.*[15] reported a patient who had progressively worsening perineal CD, despite medical and surgical treatments, in whom hyperbaric oxygen (HBO) was beneficial. Since that report, HBO has been successfully used as an adjunct to surgery and metronidazole in other patients.[16, 17]

PATIENTS AND METHODS

Patients

Ten consecutive patients (8 women, 2 men; mean age, 30 years) referred to our hospital for severe perineal CD were studied. Average duration of CD was 6.5 years, and average duration of perineal lesions was 3 years (range, 2 months-10 years). Two patients had both small bowel and colonic involvement, seven had only colonic or rectal involvement, and one had only small bowel involvement. For describing lesions we used, when possible, the Cardiff classification, recently proposed before and at the end of treatment[18] (Tables 1 and 2). All patients had received one or more medical treatments, without healing the perineal lesions. They all had had previous surgical treatment.

Hyperbaric Oxygen Treatment

Patients were treated twice a day, five days a week, in a multiplace chamber, pressurized at 2.5 absolute atmospheres. Patients breathed 100 percent oxygen through a face mask. Session duration was 2 hours starting, with 15 minutes of compression and ending with 15 minutes of decompression. Treatment was planned to include 40 sessions within four weeks.

HBO was administered concomitantly with total parenteral nutrition in three cases and in the immediate postoperative course of local surgery in four cases.

Table 1.
Clinical Data of 10 Patients

Patient No.	Age (yr), Sex	Age at Onset of Crohn's Disease (yr)	Duration of Perineal Lesions	Prior Surgical Treatments	Prior Medical Treatments	Type of Lesions
1	32, F	25	2 years	Local treatment	Azathioprine, TPN, 5-ASA, zinc	Fissure plus anovaginal fistula
2	31, F	19	6 months	Ileocolectomy, local treatment	Azathioprine, TPN, 5-ASA, zinc	Fissure plus anovulval fistula
3	36, F	32	4 years	Local treatment	TPN, metronidazole	Rectovaginal fistula
4	33, F	24	6 years	Colectomy plus proctectomy	Metronidazole, azathioprine	Proctectomy wound
5	28, F	25	27 months	Local treatment	TPN, metronidazole	Cavitating ulcer plus anovulval fistula
6	28, M	14	4 years	Small bowel resection; local treatment	Metronidazole, azathioprine	Cavitating ulcer plus high complex fistula
7	20, F	17	3 months	Left colectomy plus colostomy; local treatment	5-ASA	Fissure plus skin tags plus intersphincteric fistula
8	20, F	20	2 months	Local treatment	5-ASA	Cavitating ulcer plus perianal fistula
9	22, M	11	10 years	Left colectomy plus colostomy plus local treatment	Metronidazole, azathioprine, salazopyrine	Cavitating ulcer with extension to perineal skin plus anal stricture
10	46, F	45	2 years	Local treatment	Metronidazole, 5-ASA	Fissure plus anovaginal fistula

TPN = total parenteral nutrition; ASA = aminosalicylate.

RESULTS

Two patients discontinued HBO after a few sessions: the first one because of a bilateral eardrum perforation (patient 9) and the second one because of a bad psychologic tolerance of the treatment (patient 10).

Two patients received the complete initially defined treatment of 40 HBO sessions. Six patients discontinued HBO before the end of 40 sessions but completed at least 30 sessions: two because treatment was inefficient and four because of bad psychologic tolerance, which occurred after complete or partial healing.

At the end of the procedure, six of eight patients treated were cured, three completely and three partially (Table 2). The three patients who healed completely received HBO as an additional treatment to local surgical procedures; the first one (patient 5) suffered from an anovulval fistula and a cavitating ulcer for 27 months and was already treated with metronidazole, total parenteral nutrition, and local surgery. She received HBO as an additional treatment to local surgery (flap advancement) and total parenteral nutrition, which lead to complete healing of the fistula. The second one (patient 6) had a highly complex fistula for four years and was treated with metronidazole, azathioprine, and local surgery, which included drainage of an abscess and progressive laying open of the fistula. Despite these treatments, the fistula remained unhealed, and a progressive laying open of the fistula was then undertaken, combined with HBO, leading to a complete healing of the fistula. The third patient (patient 7) suffered from an intersphincteric fistula for three months and received HBO after progressive laying open of the fistula and a left colectomy with colostomy for severe colitis. At the end of the procedure, the perianal lesions had healed. Complete healing remained in these three patients at six-months to one-year follow-up.

Three patients were only partially cured at the end

Table 2.
Results of Hyperbaric Oxygenation in Eight Patients

Patient No.	Duration of Perineal Lesions	Active CD at the Beginning of Treatment	Associated Treatment	Number of HBO Sessions	Cardiff Classification		Global Assessment	
					Before HBO	After HBO	End of Procedure	Follow-up
1	2 years	Yes	TPN, azathioprine	36	U1a F1d S0 A1P1,2,3D2	U1a F1d S0 A1P1,2,3D1	UH	0 (recurred after 3 months)
2	6 months	No	TPN, azathioprine	30	U1A F1b S0 A3P1,2,3D1	U1a F1b S0 A3P1,2,3D1	0	0
3	4 years	No	TPN	30	U0 F2d S0 A0 P2 D2	U0 F2d S0 A0 P2 D2	0	0
4	6 years	No	None	40	No classification available	Uncomplete Healing	UH	CH (with 15 additional sessions; complete healing at 1 year)
5	27 months	No	Local surgery	36	U2a F1b S0 A0 P2 D1	U0 FO S0 A0 P2 D2	CH	CH (1 year)
6	4 years	No	Local surgery	40	U2a F2c S0 A0 P3 D1	U0 FO S0 A0 P3 D2	CH	CH (8 months)
7	3 months	Yes	Colectomy plus local surgery	33	U1b,c F1c S0 A0 P2 D1	U0 F0 S0 A0 P2 D2	CH	CH (6 months)
8	2 months	Yes	Local surgery	31	U2a F1a S0 A0 P2 D1	U1b F0 S0 A0 P2 D2	UH	CH (6 months with azathioprine)

TPN = total parenteral nutrition; UH = uncomplete healing; 0 = no result; CH = complete healing.

of HBO sessions; the first one (patient 1) had a large symptomatic anovaginal fistula, which remained unhealed despite local surgery the previous two years followed by total parenteral nutrition and metronidazole. At the end of HBO she kept a punctiform asymptomatic rectovaginal fistula. However, azathioprine had been initiated three months earlier in this case and may have overlapped with the beneficial effect of HBO. Unfortunately she recurred after three months. The second one (patient 4) had a remaining perineal wound six years after a proctectomy, despite treatments with metronidazole and zinc supplements. At the end of 40 HBO sessions, the persistent perineal sinus was nearly completely healed, and only a punctiform sinus remained (Fig. 1). She completely healed after 15 additional sessions performed five months later and remained asymptomatic at one-year follow-up. The third one (patient 8) had a persistent anal fistula after two months, which increased after progressive laying open of the lesion. The fistula was progressively replaced by an asymptomatic fissuration at the end of HBO. Azathioprine was then commenced at the end of HBO, and fissuration completely disappeared after six months of this treatment.

Two patients did not improve. The first one (patient 2) had an unhealed anovulval fistula for six months, despite treatment with total parenteral nutrition and azathioprine. She remained unhealed under a simultaneous treatment with total parenteral nutrition, azathioprine, and HBO. The second one (patient 3) had a rectovaginal fistula for the last four years, which had already been treated with total parenteral nutrition and local surgical procedures and remained unhealed. HBO combined with total parenteral nutrition did not heal her fistula.

DISCUSSION

Results of this series suggest that HBO may be helpful in treatment of severe perineal CD. Six of eight evaluable patients were asymptomatic at the end of treatment. Three completely healed, and three had their lesions significantly improved, of whom one

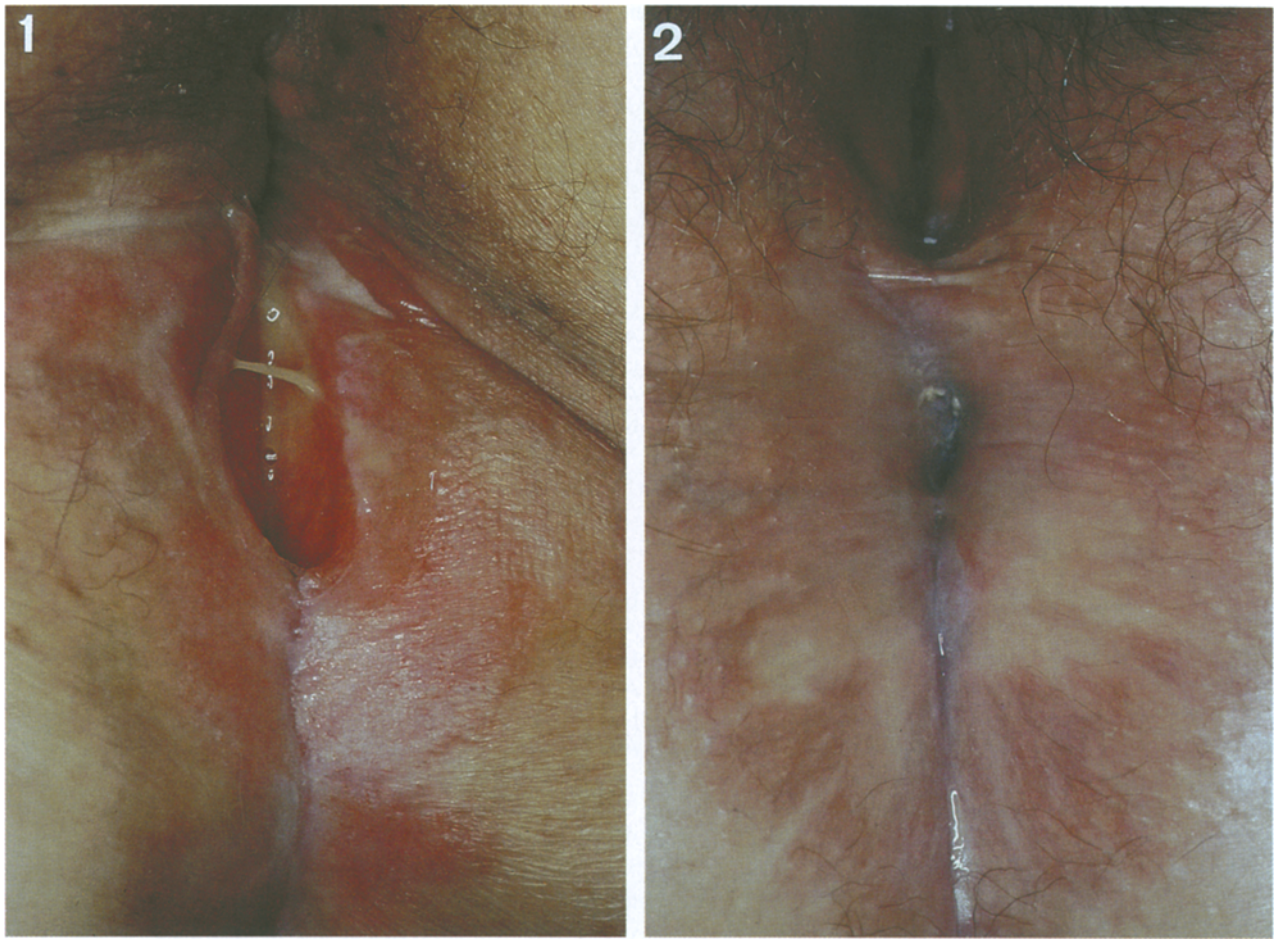

Figure 1. Perineal wound postproctectomy in patient 4 before (1) and at the end (2) of the 40 HBO sessions.

completely healed after a second course of HBO. Our patients varied significantly as far as characteristics and age of their perineal lesions, activity of contiguous visceral disease, and previous treatments. However this heterogeneity is inevitable because HBO was attempted as a last resort in patients in whom conventional treatments had failed.

Dramatic response of severe perineal and cutaneous CD to HBO was first reported by Brady *et al.*[15] in a patient who had not responded to multiple medical and surgical treatment modalities. They reported on a 48-year-old patient with a particularly severe perineal and cutaneous CD, who had been refractory to metronidazole, corticosteroids, salazopyrine, antibiotics, and surgery (colostomy, proctectomy) during an eight-year period. At the time of their report, the longest sustained remission observed in this patient had been 2.5 months. The patient became essentially asymptomatic after HBO, and the extent of her disease was minimal. Since then she has had two additional courses of HBO, the last one was completed in April 1990. She was asymptomatic ever since, did not require further treatments, and was last seen on May 1993.[19] Following this encouraging report, Lavy *et al.*[17] treated six patients with perineal CD who had not responded to salicylates, corticosteroids, metronidazole, 6-mercaptopurine, and local medications. Two of six patients experienced considerable improvement but no complete healing, two had complete healing after a course of 40 sessions each, and two were completely healed after 20 sessions each and were without recurrence after three months. Last, Nelson *et al.*[16] applied HBO as an adjunct to surgery and metronidazole in another patient whose severe perineal CD had not responded to medical and surgical therapy for nine years; these included local surgery, sulfasalazine, metronidazole, azathioprine, colostomy, then total proctocolectomy with ileostomy. HBO was combined with metronidazole, and both were integrated with staged surgical repair of the defect using debride-

ment and myocutaneous flaps. This therapy was successful and resulted in complete and sustained healing without recurrence for two years.

HBO has potential side effects such as middle ear barotrauma, sinus squeezes, and ocular, neurologic, or pulmonary effects. Frequency of these side effects was, in our previous experience, about 4 per 1,000 HBO sessions. One of our patients experienced a bilateral eardrum perforation and refused to continue treatment. More worrying potential adverse effects such as pulmonary lesions (pulmonary lesional edema potentially leading to fibrosis) and oxygen neurotoxicity never occurred with the therapeutic procedures in our patients or in the literature. The most significant limitation to HBO in our patients was bad psychologic tolerance, which lead to treatment termination after a few sessions in one patient and shortening our protocol in three others. Because good results have been observed by Lavy *et al.*[17] with a shorter course of 20 sessions, decreasing the number of sessions could improve tolerance.

How HBO works in perineal CD is unknown. Local ischemia and secondary anaerobic infection may play a role in the pathogenesis of perineal CD, and HBO may have direct effects such as bacterial killing,[20, 21] enhancement of leukocyte bactericidal activity,[22–24] fibroblasts replication, and collagen synthesis.[25] HBO is also effective in promoting capillary proliferation in poorly granulating wounds.[26] Using theses effects, HBO has been successfully used in patients with delayed wound healing, such as diabetic foot or irradiated tissue, or to prepare areas of pyoderma gangrenosum for successful skin grafts.[27–30] Furthermore, HBO may act synergistically with metronidazole as a bactericidal agent, able to eradicate purulent exudate and improve wound margin, thus permitting surgical closure.[16]

CONCLUSION

Our results of HBO in treatment of severe perineal CD are encouraging. We are thus currently pursuing our experience by trying to define the best indications and protocols. One attractive way might be to combine HBO with local surgical procedures, because we observed the best results with this combined treatment.

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