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Hyperbaric oxygen therapy for the treatment of perianal fistulas in 20 patients with Crohn's disease

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Summary

Background: Positive effects of hyperbaric oxygen on perianal fistulas in Crohn's disease have been reported.

Aim: To assess efficacy, safety and feasibility of hyperbaric oxygen in Crohn's disease patients with therapy-refractory perianal fistulas.

Methods: Twenty consecutive patients were recruited at the out-patient fistula clinic of the Amsterdam UMC. Crohn's disease patients with high perianal fistula(s) failing conventional treatment for over 6 months were included. Exclusion criteria were presence of a stoma, rectovaginal fistula(s) and recent changes in treatment regimens. Patients received treatment with 40 hyperbaric oxygen sessions and outcome parameters were assessed at Week 16.

Results: Seven women and 13 men were included (median age 34 years). At Week 16, median scores of perianal disease activity index and modified van Assche index (co-primary outcome parameters) decreased from 7.5 (95% CI 6-9) to 4 (95% CI 3-6, $P < 0.001$), and from 9.2 (95% CI 7.3-11.2) to 7.3 (95% CI 6.9-9.7, $P = 0.004$) respectively. Perianal disease activity index scores ≤4 (representing inactive perianal disease) were observed in 13/20 patients (65%). Twelve patients showed a clinical response (60%) and four (20%) clinical remission, assessed with fistula drainage assessment. Median C-reactive protein and faecal calprotectin levels decreased from 4.2 mg/mL (95% CI 1.6-8) to 2.2 (95% CI 0.9-4.3, $P = 0.003$) and from 399 μg/g (95% CI 52-922) to 31 (95% CI 16-245, $P = 0.001$), respectively.

Conclusions: We found significant clinical, radiological and biochemical improvement in Crohn's disease patients with therapy-refractory perianal fistulas after treatment with hyperbaric oxygen.

Clinical trial registration: www.trialregister.nl/trial/6489.

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1 | INTRODUCTION

Perianal fistulas are common complications in Crohn's disease, with every third patient developing at least one fistulising episode during their disease course.[1] Clinical manifestations range from painless fistula discharge to abscess formation accompanied by pelvic sepsis.[2] Spontaneous fistula closure is rare, and most patients require medical and/or surgical intervention.

Medical treatment usually consists of anti-tumour necrosis factor therapy (anti-TNF, mostly infliximab and adalimumab) with success rates up to approximately 40%.[3,4] Surgical treatment generally includes placement of a loose seton as a first therapeutic approach in order to prevent retention in the fistula tract and abscess formation. Subsequent surgical interventions aimed at closure include mucosal advancement flaps and ligation of the intersphincteric fistula tract, depending on the anatomy of the fistula tracts. Success percentages have been described in up to 60% of patients.[5,6] Unfortunately, in up to 50% of patients, the fistula does recur in due time (follow-up of 48 months).[5,6]

The use of mesenchymal stem cells is a new treatment modality in selected cases with complex fistulas; A recent study showed that closure of the internal opening with injection of stem cells around the fistula tract can achieve combined clinical and radiological (assessed by magnetic resonance imaging [MRI]) remission in 50% of patients at Week 24, compared to 34% in the placebo group.[7]

Overall, even after multidisciplinary approach, long-term success rates remain disappointing. In a large epidemiological study, only one third of patients with complex perianal fistulas achieved clinical remission at the end of follow-up (median 10 years).[8] Furthermore, a substantial part (63.8%) of these patients underwent a defunctioning ostomy. Along with a significant impact on quality of life and inflammatory bowel disease (IBD)-related work disability, perianal fistulas represent one of the biggest unmet needs in the treatment of Crohn's disease.[9,10]

Hyperbaric oxygen therapy has been suggested as a potential adjunctive treatment for patients suffering from IBD.[11] Hyperbaric oxygen therapy consists of breathing 100% oxygen under higher than normal atmospheric pressure: usually 202-253 kilopascal (equivalent to 2.0-2.5 atmosphere absolute). The hyper oxygenation and oxidative stress associated with hyperbaric oxygen therapy has been shown to result in anti-inflammatory effects, stem cell mobilisation and upregulation of growth factors.[11-13] Treatment for chronic problems (eg wound healing) usually consists of daily sessions for 6 to 8 consecutive weeks. The 'Undersea and Hyperbaric Medical Society', a nonprofit organisation that plays an important role in providing scientific and medical information on hyperbaric medicine, currently lists 14 indications for hyperbaric oxygen therapy.[14] These include late radiation tissue injuries, diabetic foot ulcers and carbon monoxide poisoning. The therapy is considered safe with few complications. Barotrauma of the ears or sinuses are among the most frequently reported side effects.[15]

Positive outcomes with hyperbaric oxygen therapy for treating perineal Crohn's disease have been reported in small case series.[11,16,17] However, patient characteristics and outcome parameters were not well defined in these studies, leading to a significant risk of bias. The objective of this prospective interventional study was to assess efficacy, safety and feasibility of hyperbaric oxygen therapy in Crohn's disease patients with therapy-refractory perianal fistulas.

2 | METHODS

2.1 | Study design

The HOT-TOPIC study is a prospective interventional (pilot) study.

The study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol has been approved by the Medical Ethical Committee (METC 2017_132) and has been published previously.[18] The trial has been registered at the Dutch Trial Registry (NL 6489/NTR 6676).

The complete follow-up period for the study is 60 weeks, with outcomes of Week 16 (ie 8 weeks after finishing hyperbaric oxygen treatment) presented in this article.

All authors had access to the study data and reviewed and approved the final manuscript.

2.2 | Population

The study has been conducted in the Amsterdam University Medical Center (UMC), location AMC. Patients were recruited at the multidisciplinary tertiary out-patient (fistula)-clinic of the IBD centre. All consecutive eligible patients were counselled for available treatment options by both a gastroenterologist and surgeon simultaneously. Patients who were eligible for the study but did not wish to undergo hyperbaric oxygen therapy were asked to serve as a control group.

All participants provided written informed consent.

Patients of 18 years or older with a confirmed diagnosis of Crohn's disease with one or more actively draining high perianal fistula (a high fistula tract is defined as transversing the upper 2/3 of the external sphincter/puborectal muscle, regardless of the number of internal and external openings) failing standard care (medical and/or surgical, defined as persisting fistula drainage in the preceding >6 months) or intolerance to standard treatment were included. Treatment regimens had to be stable for at least 6 weeks prior to starting hyperbaric oxygen treatment, that is, no starting of antibiotics, no surgical intervention except for seton placement, no addition of immunosuppressants and/or no dose changes in biologicals.

Patients with a stoma, rectovaginal fistulas, anal strictures and/or fluid collections/abscesses requiring surgical drainage were excluded, as well as patients who were unwilling to undergo seton drainage or patients with a seton in situ >12 months. Patients with proctitis were excluded, unless there were no deep ulcers seen at endoscopy. Patients who underwent a prior surgical procedure in the preceding 3 months (except from seton placement) or changes

in medical treatment (including dose and interval changes in biologicals, addition of antibiotics or immunosuppressants or switching biologics) in the preceding 6 weeks were also excluded, as well as patients who were unfit to undergo hyperbaric oxygen treatment (as assessed by the hyperbaric physician).

2.3 | Treatment

Eligible patients were treated with 40 daily hyperbaric oxygen sessions on working days, that is, for a duration of 8 weeks in total. Sessions consisted of administration of a total of 80 minutes of 100% oxygen at 243-253 kilopascal. This treatment profile was similar to the normal clinical hyperbaric oxygen protocol in the Netherlands and remains well within non-decompression and oxygen toxicity limits. Hyperbaric oxygen treatment was provided in the hyperbaric unit of the Amsterdam UMC as well as in seven hyperbaric chambers across the Netherlands.

Treatment was started directly after enrolment and after investigation of fitness for hyperbaric oxygen treatment by the hyperbaric physician. All patients were treated in a multiplace chamber. If patients received less than 35 hyperbaric oxygen sessions or in case they missed more than two consecutive sessions (excluding weekends) they were replaced in the study or the treatment regimen was started anew.

If patients did not have adequate seton drainage at the start of hyperbaric oxygen therapy, one or more setons were placed in theatre before the start of treatment. Seton removal was planned after 30 sessions (ie at Week 6 after starting hyperbaric oxygen therapy) in order to allow for fistula closure. The medical treatment regimen patients received for their Crohn's disease remained unchanged in principle, but if necessary a change in medication (such as addition of antibiotics) could be made at the discretion of the primary physician.

Patients who were eligible to participate but did not wish to undergo hyperbaric oxygen therapy were asked to serve as a control group. The control group was added to the study in order to keep track of the feasibility of hyperbaric oxygen therapy, and in order to assess baseline characteristics and the disease course of patients who declined hyperbaric oxygen treatment. Patients in the control group continued to receive standard care (medical and/or surgical) as deemed suitable by their primary physician during their visits at the fistula clinic.

2.4 | Endpoints

The co-primary outcome parameters were improvement in perianal disease activity index (PDAI) and improvement on magnetic resonance imaging (MRI) as measured by the (modified) van Assche index at Week 16 (ie 8 weeks after finishing hyperbaric oxygen treatment).[19] For the PDAI, inactive perianal disease was defined as a score of 4 or less. [20]

Secondary outcome parameters included clinical response and remission at Week 16 as measured by the fistula drainage assessment, with clinical response defined as a reduction of ≥50% in the number of draining fistulas and clinical remission defined as the absence of draining fistulas upon gentle finger compression.[21]

Biochemical changes in C-Reactive Protein and faecal calprotectin levels were assessed at Week 16, as well as the proportion of patients with normal values of C-reactive protein (5 mg/L) and faecal calprotectin values below the cut-off score for remission of IBD (250 μg/g).[22]

For patient-reported outcomes, scores of a visual analogue scale (VAS, that records the respondent's self-rated health on a scale from 0 to 100, with higher scores indicating higher quality of life), the Inflammatory Bowel Disease Questionnaire (IBDQ, range 32-224 with higher scores reflecting better quality of life) and a validated decision regret scale (scale 0-100 with higher scores reflecting higher regret of the decision to undergo hyperbaric oxygen therapy) were assessed at Week 16.[23,24] For the IBDQ, the proportion of patients with a relevant clinical response (increase of ≥27 points) and the proportion of patients in remission (score of ≥168) were also assessed.[25] Patients were also asked to answer “yes” or “no” on the question if they felt their fistula(s) had improved due to hyperbaric oxygen treatment.

Furthermore, changes in use of concomitant medication, re-interventions and adverse events during the study (16 weeks) were reported. At the end of hyperbaric oxygen treatment, in addition to assessment of any unsolicited adverse events, patients were specifically asked about common side-effects of hyperbaric oxygen therapy, that is, complaints of trouble equalising, visual changes and fatigue (solicited events).

Clinical outcomes were assessed by the treating physician of the patients (gastroenterologist and/or surgeon) at the out-patient fistula clinic. The (modified) van Assche scores were assessed in a nonrandom order by an independent abdominal radiologist with 26 years of experience in MRI of fistulising Crohn's disease who was blinded to clinical outcomes. Adverse events during hyperbaric oxygen treatment were assessed by the supervising hyperbaric physician. None of the assessors were blinded to the intervention.

In the control group, the same outcome measures were assessed, except for MRI and biochemical response. Reasons for refusal to undergo hyperbaric oxygen treatment were noted. Assessment of outcome parameters was performed at the same time point as for the hyperbaric oxygen therapy group, at Week 16.

2.5 | Sample size and statistical analysis

As no spontaneous healing was expected in this therapy-refractory group, the outcome of 20 patients after hyperbaric oxygen therapy was estimated to give an indication of the success of hyperbaric oxygen therapy and should also be enough to determine the feasibility and possible efficacy of the treatment.

The number of patients in the control group was unlimited.

All parameters were tested for a two-tailed significance of $P < 0.05$ and were assessed using nonparametric tests. The co-primary endpoints PDAI and MRI are (semi-)continuous variables and were analysed with the Wilcoxon signed rank test. Differences in (semi-) continuous variables, such as the patient-reported outcomes and C-reactive protein/faecal calprotectin, were analysed using the Wilcoxon signed rank test.

3 | RESULTS

3.1 | Inclusion and baseline characteristics

Screening for eligible patients took place between October 2017 and June 2019. In total, 29 eligible patients were counselled. All patients gave informed consent to participate: 21 patients accepted treatment with hyperbaric oxygen (72%) and 8 patients were included in the control group. One patient in the hyperbaric oxygen therapy group withdrew from the study after five hyperbaric oxygen sessions because of inadequate seton drainage and was replaced by another patient. Twenty patients in the hyperbaric oxygen therapy group and eight patients in the control group completed the study and follow-up (16 weeks). A study CONSORT flowchart is available in Appendix S1.

Patient baseline characteristics for the hyperbaric oxygen therapy group are shown in Table 1. The median duration of the current active perianal fistula(s) was 4 years. Luminal disease activity (based on the results of the last endoscopy in case of stable luminal complaints) was present in the ileum (n = 3), right colon (n = 1), left colon and sigmoid (n = 1) and rectum (n = 2). Eighty-five per cent of patients used concomitant medication: most patients used combination therapy consisting of anti-TNF combined with an immunomodulator (n = 9). Other medication regimens included anti-TNF monotherapy (n = 4), anti-TNF therapy combined with chronic antibiotic use (n = 1), vedolizumab (n = 1), ustekinumab (n = 1) and mesalamine (n = 1). A total of 17 of 20 patients (85%) had the last change in medication more than 6 months before the start of hyperbaric oxygen therapy, the remaining three patients had a change in medication less than 6 months before the start of hyperbaric oxygen therapy (but more than 6 weeks as required per study protocol). Including previous treatment, 19 of 20 patients received anti-TNF therapy at some point during the course of their perianal disease. Four patients had a previous surgical closure attempt for their fistula: three mucosal advancement flaps and one bioprosthetic plug. One of these patients also had a temporary diverting ostomy. Five patients had four or more external fistula openings: three patients had four openings, one patient had five openings and another patient seven openings. All patients started with one or more setons in place after examination under anaesthesia (as required per study protocol) to assure adequate drainage before the start of hyperbaric oxygen therapy; the majority of patients (11 of 20) had this procedure performed more than 6 months before the start of hyperbaric oxygen therapy. There were no comorbidities relevant to the perianal disease or hyperbaric treatment.

TABLE 1 Baseline characteristics of patients undergoing hyperbaric oxygen therapy

Characteristics	n = 20
Age (median age, IQR)	34 (24-49)
Gender at birth (number of patients)	
Male	13 (65%)
Female	7 (35%)
Active smoking (number of patients)	4 (20%)
Luminal disease activity present (number of patients)	5 (25%)
Concomitant use of medication	17 (85%)
Anti-TNF therapy	14 (70%)
Years disease duration Crohn's disease (median, IQR)	12 (4-19)
Years disease duration perianal Crohn's disease (median, IQR)	7 (3-12)
Years disease duration current fistula (median, IQR)	4 (2-12)
Previous surgical closure (number of patients)	4 (20%)
Number internal openings (number of patients)	
1	15 (75%)
2	4 (20%)
3	1 (5%)
Number of external openings (number of patients)	
1	7 (35%)
2	5 (25%)
3	3 (15%)
4 or more	5 (25%)

Abbreviation: IQR, interquartile range.

3.2 | HBO and seton removal

Three patients received less than 40 sessions (37, 38 and 39 sessions); in two cases this was due to personal and unrelated issues and in one case a common cold was the reason for early termination of the treatment. All other patients completed 40 consecutive sessions. In 18 of 20 patients, all setons were removed during hyperbaric oxygen treatment, after a median of 26 sessions (range 20-30). In the remaining two patients, it was deemed there was still too much induration to remove all setons during hyperbaric oxygen treatment: one patient had four setons of which two were removed during hyperbaric oxygen treatment and two were still in situ at follow-up. The other patient had four setons of which three were removed during hyperbaric oxygen treatment and the last seton at follow-up.

3.3 | Co-primary outcome parameters: PDAI and (modified) van Assche index

Median PDAI and (modified) van Assche scores are depicted in Table 2. Individual changes in scores can be found in Figure 1.

The median PDAI score decreased from 7.5 (95% CI 6-9) to 4 (95% CI 3-6, $P < 0.001$) at Week 16, reflecting an improvement in

TABLE 2 Perianal disease activity index, (modified) van Assche scores and patient-reported outcomes at baseline and Week 16 of patients treated with hyperbaric oxygen therapy

	Baseline		Week 16		Statistical significance
	Median	95% CI	Median	95% CI	*P*-value
Perianal disease activity index[a]	7.5	6-9	4	3-6	<0.001
Modified van Assche index[b]	9.2	7.3-11.2	7.3	6.9-9.7	0.004
Original van Assche index[c]	13	12-15	12	10-13	0.005
VAS score[d]	67.5	61-78	70	60-76	0.26
IBDQ score[e]	169	141-191	183	167-199	0.001
Decision regret scale score[f]	NA	NA	15	5-25	NA

Note: CI, confidence interval; VAS, visual analogue score; IBDQ, inflammatory bowel disease questionnaire; NA, not applicable.

[a]The perianal disease activity index evaluates five items: fistula production, pain and restriction of activities, limitation of sexual activities, type of perianal disease and severity of induration. Every category includes a scale ranging from 0 to 4 points, higher scores representing higher disease activity. The total score can range from 0 to 20 points.

[b]The modified van Assche index consists of five items: extension, hyperintensity on T2-weigthed images, rectal wall involvement, inflammatory mass and dominant feature of the primary tract and extensions. The total score can range from 0 to 19.5 points, with higher scores representing more severe perianal disease.

[c]The original van Assche index consists of six items: number of fistula tracts, location, extension, hyper intensity on T2-weighted images, collections and rectal wall involvement. The total score can range from 0 to 22 points, with higher scores representing more severe perianal disease.

[d]The VAS score records the respondent's self-rated health on a scale from 0 to 100, with higher scores indicating higher quality of life.

[e]The IBDQ is a 32-item questionnaire concerning four dimensions of quality of life in patients with inflammatory bowel disease (bowel function, emotional status, systemic symptoms and social functioning), with scores ranging from 32 to 224, with higher scores indicating a better quality of life.

[f]The decision regret scale consists of five statements that measure distress or remorse after a health-care decisions. The scale ranges from 0 to 100, with higher scores reflecting higher regret of the decision.

perianal disease. Inactive perianal disease, defined as a PDAI score of 4 or less, was achieved in 13 patients (65%). [20]

The median time between the baseline MRI and the start of hyperbaric oxygen treatment was 28 days. The median modified van Assche and original van Assche scores decreased from 9.2 (95% CI 7.3-11.2) to 7.3 (95% CI 6.9-9.7, $P = 0.004$) and from 13 (95% CI 12-15) to 12 (95% CI 10-13, $P = 0.005$), respectively, at Week 16. Items of the MRI indices that were most reactive to change after hyperbaric oxygen treatment were inflammatory items (ie rectal wall involvement and inflammatory mass), as well as the dominant feature of the primary tract and extensions. Three patients had a fibrotic fistula complex at follow-up. Examples of MRI images showing change in these respective items can be found in Figures 2 and 3. Counts and changes in the individual scoring items of the original and modified van Assche score are available in Appendix S1 (Table S1).

3.4 | Secondary outcome parameters

3.4.1 | Fistula drainage assessment

Twelve of 20 patients (60%) showed a clinical response as measured by the fistula drainage assessment at Week 16, and 4 of 20 patients (20%) were in clinical remission. In total, 50 external fistula openings were present at baseline, of which 24 were closed at Week 16 (48%).

3.4.2 | Biochemical response

The median C-reactive protein value at baseline was 4.2 mg/mL (95% CI 1.6-8 mg/mL) which decreased to 2.2 mg/mL (95% CI 0.9-4.3 mg/mL) at Week 16, $P = 0.003$. Eleven patients had normal baseline C-reactive protein values, and 15 patients had normal values at Week 16. For faecal calprotectin, the median value decreased from 399 μg/g (95% CI 52-922 μg/g) to 31 μg/g (95% CI 16-245 μg/g) at Week 16, $P = 0.001$. Nine patients had values of faecal calprotectin indicating remission at baseline, and 16 patients had these values at Week 16. Figure 4 shows the individual C-reactive protein and faecal calprotectin values of patients at baseline and Week 16.

3.4.3 | Patient-reported outcomes

The median VAS score increased from 67.5 (95% CI 61-78) to 70 (95% CI 60-76, $P = 0.26$) at Week 16. The median IBDQ score at baseline was 169 (95% CI 141-191) and increased to 183 (95% CI 167-199, $P = 0.001$). Based on the IBDQ scores, 11 patients were in clinical remission at baseline, and three additional patients achieved clinical remission at Week 16 (14 patients in clinical remission in total). Four patients had a relevant clinical response, indicated by an increase in score of ≥27 points. The median score of the decision regret scale was 15 (IQR 5-25). Fourteen of 20 patients (70%) answered "yes" on the dichotomous question if

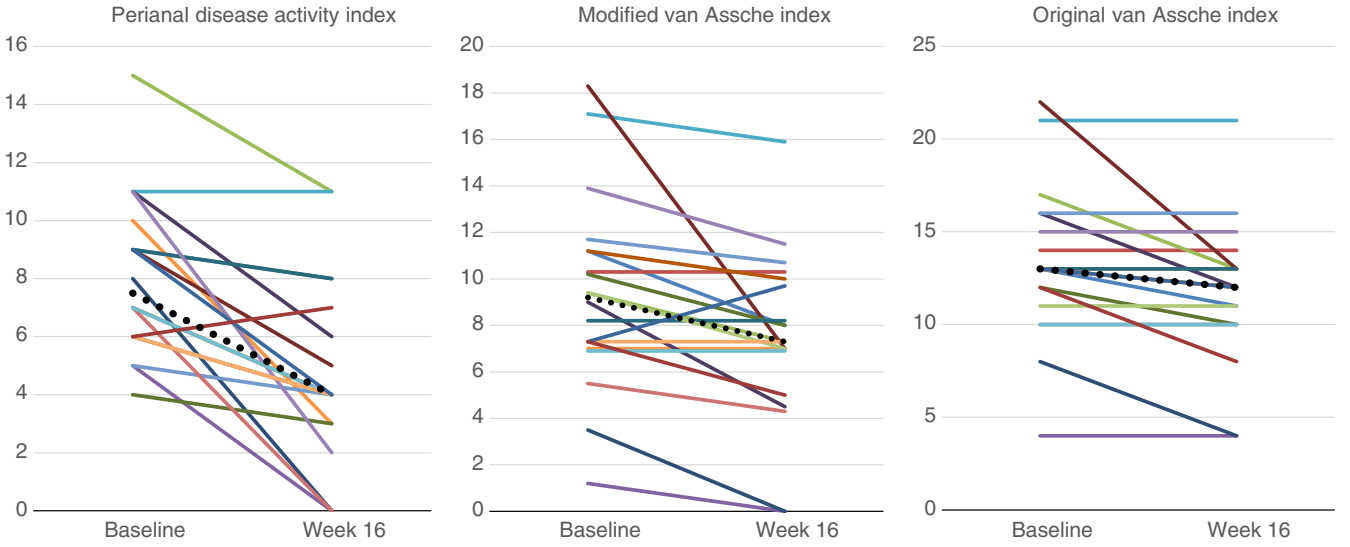

FIGURE 1 Individual median perianal disease activity index, modified van Assche and original van Assche index scores at baseline and Week 16 in patients treated with hyperbaric oxygen therapy (median scores are indicated by dotted black line)

patients felt their fistula(s) had improved at Week 16. The median VAS, IBDQ and decision regret scale scores can also be found in Table 2.

3.5 | Adverse events

3.5.1 | Hyperbaric oxygen therapy-related adverse events

One patient withdrew from the study after five hyperbaric oxygen sessions due to ongoing perianal complaints and abscess formation due to inadequate seton drainage. After multiple surgeries to improve drainage that were unsuccessful she underwent an ostomy and was replaced in the study.

In the 20 patients who completed hyperbaric oxygen treatment, there were 10 unsolicited events in eight patients of trouble equalising middle ear pressure during hyperbaric oxygen therapy. Subsequent otoscopy showed signs of mild-to-moderate barotrauma in five of these eight patients, with no perforation of the eardrums. Three patients required tympanostomy tubes to complete the course of treatment.

One other patient complained of abdominal pain during hyperbaric oxygen therapy, with no residual complaints outside of the hyperbaric chamber and no relation to pressure differences. An extensive evaluation including laboratory tests showed no abnormalities, and no relation to luminal Crohn's disease was found. One patient had gastrointestinal complaints (vomiting, diarrhoea) for 1 day during hyperbaric oxygen therapy, with complete resolution of complaints the next day.

Solicited events during hyperbaric oxygen therapy were fatigue (5 patients) and visual changes (2 patients), which were all reversed after the treatment.

3.5.2 | Re-interventions and medical changes related to fistulas

There were no surgical (re-)interventions during hyperbaric oxygen therapy and/or the study (16 weeks), including no drainage of abscess, seton placement or deviating colostomy. One patient had an increase in perianal complaints during the first week of hyperbaric oxygen therapy for which an MRI was performed (no signs of abscess formation was seen) and antibiotics were started. Because of ongoing complaints, the patient had an inspection under anaesthesia in theatre, but no abnormalities were found and no surgical intervention took place.

Apart from antibiotic treatment in this patient, two other medical changes took place. In one patient, the infliximab dose was increased and in another patient the thiopurine agent was stopped (request of the patient).

3.6 | Control group

The control group consisted of eight patients, five female and three male patients. The median age was 35 (IQR 24-41), and none of the patients were active smokers. The median disease duration was 6 years (IQR 1-24), and the median disease duration of the current fistula was 2 years (IQR 1-7). Five patients had one internal opening and three patients had two internal openings at enrolment. The median PDAI at baseline for the control group was 8.5 (IQR 5.3-10.8), and the median IBDQ 145 (IQR 90.5-183.5).

The main reasons for refusal of hyperbaric oxygen treatment were interference of the treatment with patients' personal lives such as their jobs and families (three patients), patients having too little complaints for the amount of time that should be invested to undergo the treatment (three patients) and hyperbaric

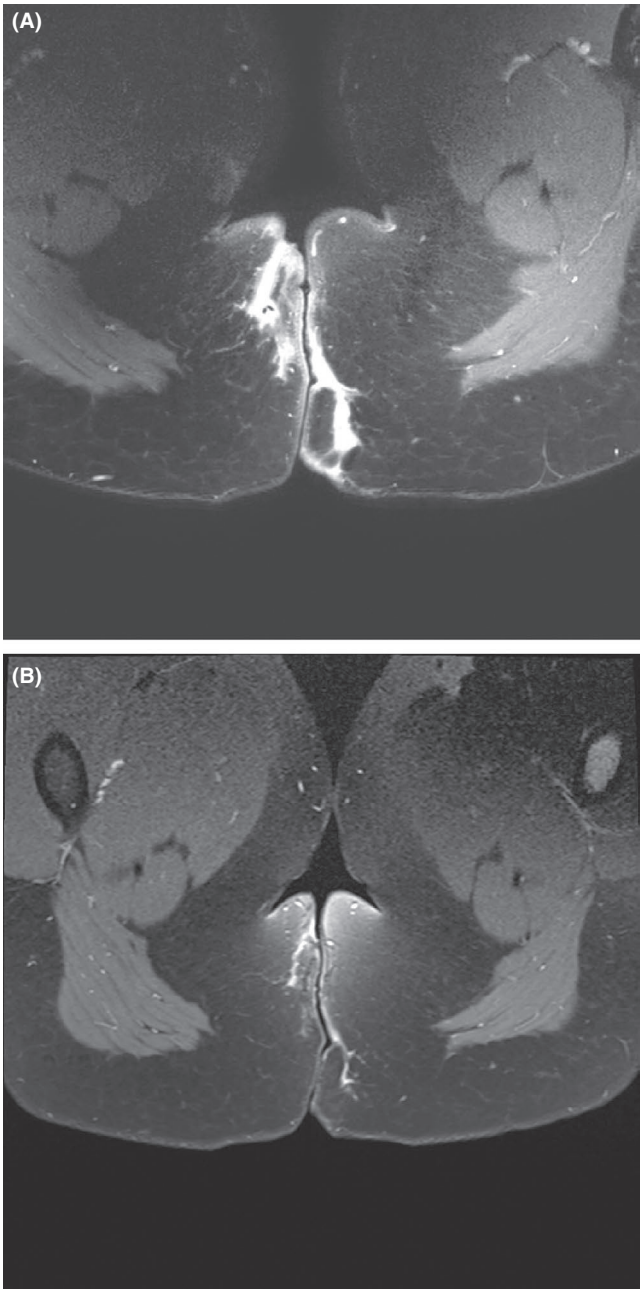

FIGURE 2 Axial oblique T1-weighted MRI imaging at baseline (A) and Week 16 (B) of a patient with a decreased (modified) van Assche score on the item 'inflammatory mass' after treatment with hyperbaric oxygen therapy

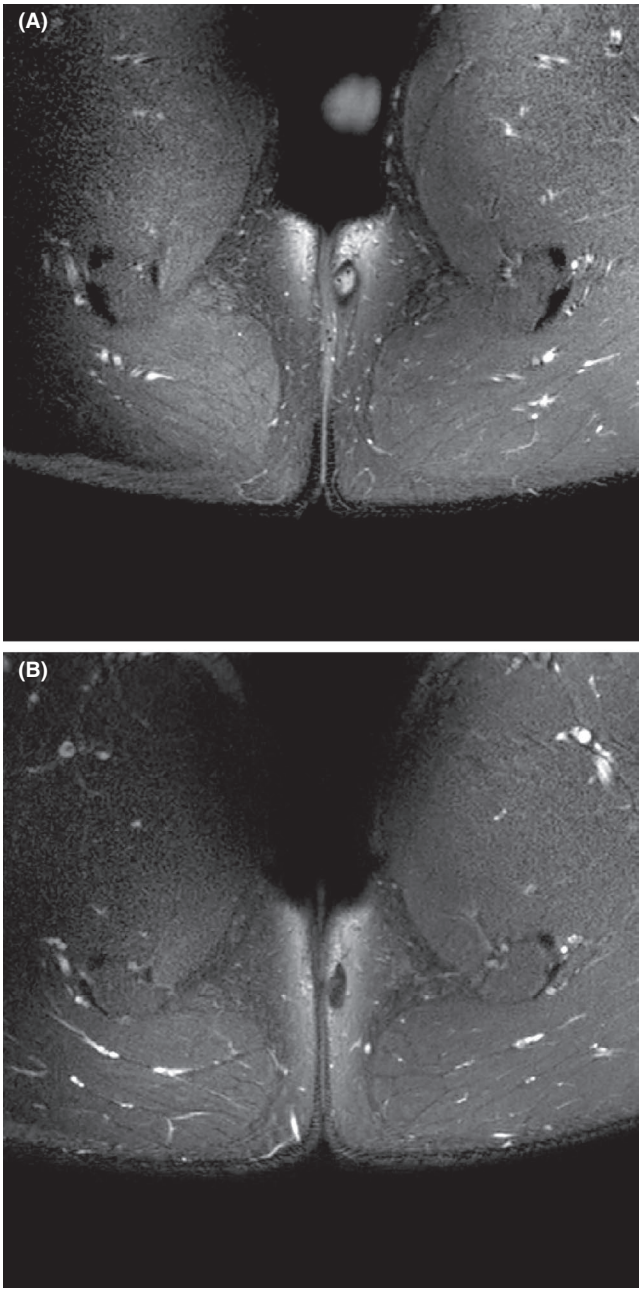

FIGURE 3 Axial oblique T2-weighted MRI imaging at baseline and Week 16 of a patient with a decrease modified van Assche score on the item 'dominant feature of primary tract and extensions', being predominantly fibrotic after hyperbaric oxygen therapy

oxygen therapy being too experimental/not proven effective (two patients).

Three patients in the control group had a ligation of the intersphincteric fistula tract that was performed during the follow-up period (16 weeks). Another patient was scheduled for a ligation of the intersphincteric fistula tract, but during surgery it was decided to perform a fistulotomy. In the remaining four patients, all setons were left in situ during follow-up. One of them was treated with a course of antibiotics because of perianal complaints. No other medical changes took place.

The median PDAI score for all patients in the control group decreased from 8.5 at baseline (95% CI 5-12) to 6 (95% CI 1-11, $P = 0.04$) at Week 16. The median VAS score increased from 60.5 (IQR 25-80) to 63 (95% CI 35-80) and the median IBDQ score increased from 145 (95% CI 78-198) to 154 (95% CI 86-214), both of which were not statistically significant ($P = 0.60$ and 0.12 respectively).

In the patients who did not receive a surgical re-intervention (n = 4), the PDAI decreased from 6.5 at baseline (IQR 5.25 - 10) to 6 (IQR 3.5 - 10) at Week 16. There were no patients with clinical

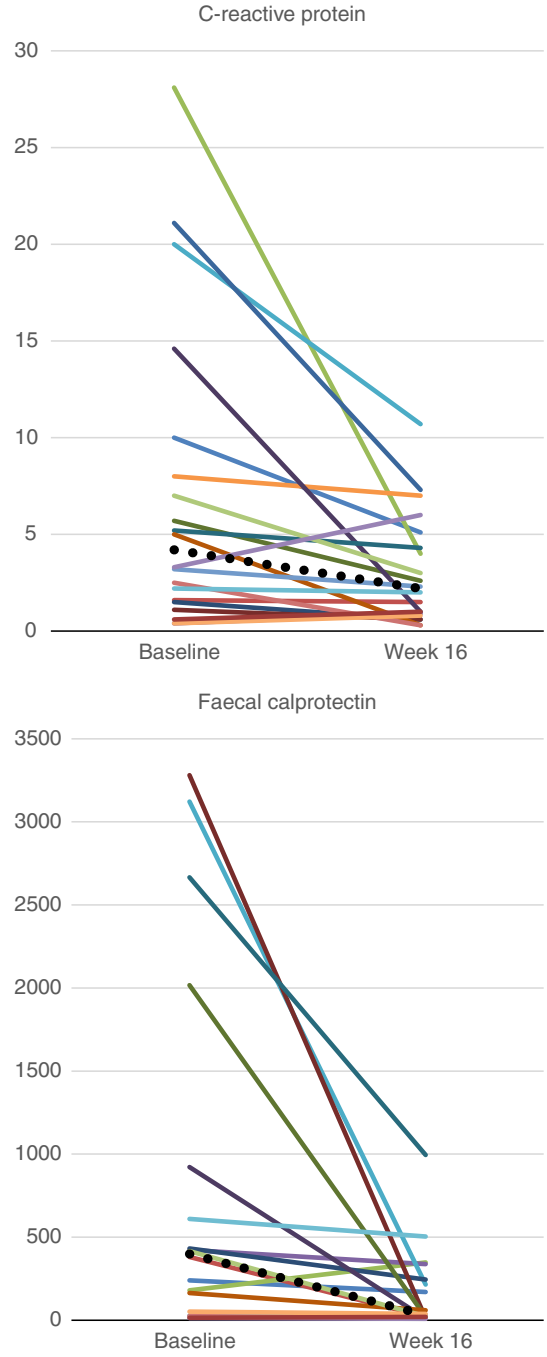

FIGURE 4 Individual C-reactive protein and faecal calprotectin values at baseline and Week 16 in patients treated with hyperbaric oxygen therapy (median scores are indicated by dotted black line)

response or remission as assessed by the fistula drainage assessment. None of the patients had a relevant clinical response based on their IBDQ score (ie an increase in score).

In the patients who underwent a surgical intervention (n = 4), the median PDAI decreased from 10 at baseline (IQR 6.25-11.5) to 5.5 (IQR 1.75-7) at Week 16, with two patients achieving inactive perianal disease (PDAI score ≤4). As assessed by the fistula drainage assessment, one patient was a clinical responder, and three patients were in clinical remission at Week 16. One patient had a relevant clinical response (increase in IBDQ score of ≥27) at Week 16.

4 | DISCUSSION

The patients evaluated in the HOT-TOPIC trial were Crohn's disease patients with difficult-to-treat perianal fistulas with a median disease duration of 4 years. At Week 16 a significant improvement was found in the co-primary outcomes (PDAI and the (modified) van Assche index), with 65% of patients having an inactive perianal disease after treatment based on cut-off scores of the PDAI that were previously published.[20] The different MRI items that were scored showed improvement in inflammatory aspects as well as fibrosis of the fistula complex in three patients. Using the fistula drainage assessment, 60% of patients had a clinical response at Week 16 and 20% were in remission. Furthermore, significant biochemical improvements were seen, paralleled by improved patient-reported outcome measures. Overall, hyperbaric oxygen treatment was well tolerated and it turned out to be feasible.

Although comparison of the results of the HOT-TOPIC trial to those of other trials concerning fistulas should be approached with caution (given the differences in trial design, study population and outcome parameters), the results for our therapy-refractory patients are highly encouraging, especially in the light of the success rates of current treatment modalities for Crohn's fistulas as presented in the introduction. In the PISA trial that was recently performed by our group, treatment outcomes among chronic seton drainage, anti-TNF therapy and surgical intervention were compared in 94 patients.[26] Patients had a mean PDAI score between 4 and 5 at 6-month follow-up in all three groups, which is comparable to the median PDAI score found in the HOT-TOPIC trial. The PISA trial, however, involved patients with new or recently recurrent fistulas. Furthermore, the median duration of the perianal disease was shorter (1-2 years) in patients who participated in the PISA trial, and their fistulas were also less complex (median of one external opening and exclusion of patients with multiple internal openings). In contrast, the patients in the HOT-TOPIC trial were therapy-refractory and in some cases defunctioning colostomy was the only other treatment option left available. Patients will continue to be followed until Week 60 in order to assess the durability of these results.

A statistically significant drop in PDAI score was also seen in the control group, which can be mostly attributed to the four patients undergoing a surgical intervention. One patient was unexpectedly eligible for a fistulotomy, with much higher chances of success than is usual for complex fistulas in Crohn's disease patients.[27] The other three patients had a ligation of the intersphincteric fistula tract, with two having clinical remission at Week 16 after the intervention. In the hyperbaric oxygen therapy group, however, four patients already had an unsuccessful surgical intervention and another five patients were not eligible for surgery due to multiple internal openings. This indicates that the control group is not directly comparable to the

hyperbaric oxygen therapy group. Future trials can help determine the position of hyperbaric oxygen therapy with regards to surgery, as well as the efficacy compared to surgical and/or medical interventions.

Unfortunately, there is no value for the minimum clinically important difference for both the PDAI and the MRI indices, and therefore the proportion of responding patients could not be determined using these co-primary outcomes. Although the fistula drainage assessment has been used as a primary outcome in several trials, "gentle finger compression" is investigator dependent and has been shown to not always reflect healing of the underlying fistula tract.[28] Hence, radiological imaging could give additional information on fistula healing. However, there is no reference standard for measuring radiological response. A recent trial investigated the use of mesenchymal stem cells in perianal fistulas in Crohn's disease and defined radiological remission as absence of collections larger than 2 cm, while other trials reported scores of the original van Assche index.[7,28] At the time of the design of the HOT-TOPIC trial, the modified van Assche index turned out to have higher inter-rater reliability compared to the original van Assche index.[19] Meanwhile, another MRI index has been published (the MAGNIFI-CD), which has further improved existing items of previous indices as well as adding a new one (fistula length).[29] External validation of this instrument is needed before it can be used as an outcome measure in clinical trials. The need for a reliable outcome measure for perianal fistulas was endorsed at the Fifth Scientific Workshop of the European Crohn's and Colitis Organization.[28]

Assessing feasibility of hyperbaric oxygen treatment was an important objective. Feasibility of hyperbaric oxygen treatment in IBD patients has been a problem in earlier trials, and because hyperbaric oxygen treatment is demanding for patients concerns were raised that it might not be a manageable treatment option for fistula patients.[30] Patients who refused hyperbaric oxygen treatment were asked to serve as a control group in order to assess reasons for refusal, baseline characteristics and the disease course, with only minimal effort to participate (completion of questionnaires at baseline and Week 16, no laboratory findings or MRI). Only eight of 29 patients refused to undergo hyperbaric oxygen treatment. Based on these observations, we conclude that this treatment approach is feasible for Crohn's disease patients with therapy-refractory fistulas. Due to the small number of patients who were included in the control group and allocation based on patient preference a meaningful comparison in outcomes between both groups could not be made.

A randomised, controlled trial (RCT) seems warranted based on the results of this study. However, a traditional RCT has several downsides when it comes to internal and external validity in fistula patients that often have a distinct preference for their treatment.[26] Given the specific nature of the hyperbaric oxygen treatment, a patient preference model or Trial within Cohorts (TwiCs) design might be more appropriate.[31,32] It might also be interesting to investigate different approaches using hyperbaric oxygen therapy, such as treatment of patients with new fistulas (instead of therapy-refractory ones) or pre- and post-operative treatment with hyperbaric oxygen therapy around definitive surgical closure.

In the HOT-TOPIC trial, seton removal was planned after 30 hyperbaric oxygen sessions, which was decided at the discretion of the treating physician. We found that clinical improvement and epithelisation of fistula tracts was already seen after 15 to 20 hyperbaric oxygen treatments, and that setons could be removed earlier than expected. Based on these observations, future trials might assess patients at a weekly interval and setons should be removed as soon as clinical symptoms such as pain and production improve, and when epithelisation of the fistula tract occurs with no signs of induration at physical examination.

Five of the 20 patients treated with hyperbaric oxygen therapy (25%) had an adverse event with signs of mild-to-moderate middle ear barotrauma on otoscopy, with three patients requiring tympanostomy tubes to complete the course of treatment. This is a relatively high number of otologic adverse events compared to other studies using hyperbaric oxygen therapy in IBD patients, as well as in patients undergoing hyperbaric oxygen therapy for other indications.[11,15] Although there were no residual complaints during follow-up and decision regret as measured in the study was low, the risk of barotrauma should be discussed with patients before treatment and adverse events should be monitored carefully in future studies.

One of the strengths of this study is that a true consecutive series of patients in a large IBD centre was included. Secondly, concomitant medication was kept stable 6 weeks before starting hyperbaric oxygen treatment and during the study period, which reduced the potential risk of measuring effects of other treatments/interventions. Despite careful consideration of the concomitant medical regimen (including evaluation of adequate trough levels of anti-TNF therapy before inclusion in the study), an increase in dose of infliximab was made by an external gastroenterologist in one patient during hyperbaric oxygen therapy. This patient, however, did not have an improvement in PDAI, MRI scores and/or the fistula drainage assessment at follow-up, and was considered a nonresponder to hyperbaric oxygen treatment. A limitation of the study is the lack of a randomised control group, which limits the ability to establish a true causal effect of hyperbaric oxygen treatment on the positive results that were found. These could have been caused by other factors such as late effects of medication, although this seems unlikely given that a high proportion of patients (17 of 20) had a stable dose of concomitant medication for at least 6 months before the start of hyperbaric oxygen therapy (ie far longer than the 6 weeks that were required for inclusion in the study). Nine of 20 patients had an examination under anaesthesia with seton placement within 6 months before the start of hyperbaric oxygen therapy, as adequate drainage was a requirement for inclusion in the study. It is possible that this procedure contributed to improvement in some outcome parameters, although to our knowledge there is no literature that suggests that examination under anaesthesia with seton placement (and no other surgical intervention) could lead to actual fistula healing. Furthermore, given the therapy-refractory nature of the patient population, all patients had multiple examinations under

anaesthesia in the past without sufficient improvement. Another limitation of the study is that the assessment of MRIs was done in a nonrandom order and this might introduce bias, although the radiologist was blinded to all other findings. In a future, larger trial assessment in random order might be preferred to exclude this risk of bias. Random assessment, however, comes with logistic issues that should be taken into consideration: the index evaluates the "primary tract", and this tract can be different between baseline and follow-up (eg in case one of two tracts has healed at follow-up, and a secondary tract at baseline becomes the primary tract at follow-up).[19] Scoring in random order might therefore lead to assessing the wrong fistula which may introduce another bias.

In conclusion, this study shows that a clinical, radiological and biochemical improvement was found after hyperbaric oxygen therapy in Crohn's disease patients with therapy-refractory fistulas, and that the treatment was feasible and tolerated well. Future controlled trials are needed to confirm these findings.

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AUTHORSHIP

Guarantor of the article: CAL.

Author contributions: CAL, KBG, CJB, ML, JS, WAB, GDH and RAH contributed to the study conception, design and data collection. CAL, KBG, CJB, ML, WAB and GDH were involved in participant recruitment. CAL, KBG, CJB, GDH and RAH were involved in the analysis of the results. CAL drafted the manuscript and all other authors contributed to the manuscript with important intellectual content.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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