Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 7998 - 8009
Received 16 February 2021; Accepted 08 March 2021.

Role of Hyperbaric Oxygen as an Adjuvant Therapy in Severe Ulcerative Colitis Patients

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ABSTRACT

Ulcerative colitis (UC) is a chronic, inflammatory bowel disease (IBD); characterized by abdominal pain, bloody diarrhea and several extra-intestinal manifestations. Evidence has accumulated that hyperbaric oxygen therapy (HBOT) also has potent anti-inflammatory effects and may normalize oxygen levels in ischemic tissues. The aim of this study was to evaluate the efficacy of hyperbaric oxygen (HBO) as an adjuvant therapy in severe UC patients. A randomized controlled trial was conducted on 20 Egyptian patients with severe UC according to truelove and witt's criteria divided into two groups each one composed of 10 patients: the first one received 10 sessions of HBOT 5 times per week for 2 weeks plus 400 mg hydrocortisone and intravenous (IV) fluids while the second one received 400 mg hydrocortisone plus IV fluids with follow up of inflammatory markers for both groups as erythrocyte sedimentation rate (ESR), C Reactive protein (CRP), Fecal calprotectin at day 1, 3, 7 and 14 of the study and follow up of their Rectal bleeding score (RBS), Stool frequency score(SFS) and Mayo endoscopic score (MES) to assess therapeutic effect of HBOT. Our results showed significant decrease in ESR, CRP, faecal calprotectin, RBS, SFS and MES levels in group I when compared to group II at day 14 of the study. So we concluded that hyperbaric oxygen therapy has an effective and safe effect for severe UC patients beside conventional therapies to avoid second lines therapy.

Keywords
Ulcerative colitis, Hyperbaric oxygen, Fecal calprotectin, Inflammatory bowel disease, Erythrocyte sedimentation rate, Mayo endoscopic score.

Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disease involving the colon, characterized by relapsing and remitting mucosal inflammation [1]. Its peak age of onset is 30–40 years old, men and women are affected equally.The main symptoms of UC include bloody diarrhea with rectal urgency and tenesmus. Although the etiology of UC remains unclear but many theories revealed environmental factors, and less likely intestinal dysbiosis in genetically susceptible individuals, but increasing evidence suggests that it is an autoimmune condition [2].

The therapeutic target of UC was recommended as clinical and endoscopic remission. Recently, accumulating evidence suggests that histological remission more effectively reduces relapse, corticosteroid use, and hospitalization. Better long-term outcomes are associated with histological remission than with mucosal healing. Therefore, histological remission has also been proposed as a target for the treatment of UC [3]. Severe UC is a medical emergency characterized by>6 bloody stools/day with one of the following: tachycardia >90 beat per minute, fever>37.8°C hemoglobin<10.5 gm/dL, and/or ESR>30 mm/hour (Truelove and Witt's criteria), other indices for defining severity include modified Mayo's classification which is a combination of clinical and endoscopic finding [4].

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Biopsy is the gold standard for detecting and grading histological activity of UC. However, biopsy is invasive and may cause bleeding complications. Since the heterogenous distribution of inflammatory changes exists among different sample sites, the risk of sampling error creates additional challenges. Therefore, a non-invasive biomarker capable of surveillance of histological activity of UC would be helpful in clinical practice [1].

Endoscopic mucosal healing, defined as a Mayo endoscopic subscore (MES) ≤ 1, should be the therapeutic target in patients with UC as it has been shown to be associated with sustained clinical remission, decreased rate of colectomy and reduced risk of colorectal cancer. However, recent studies revealed that targeting MES 0 rather than MES ≤ 1 could decrease the risk of relapse in patients with UC. There is also growing evidence that persistent active microscopic inflammation is associated with increased risk of disease relapse, colectomy or colorectal cancer [5].

Calprotectin is a calcium binding protein present predominantly in neutrophils with antimicrobial and antiprolipherative activities. Calprotectin concentration is higher in feces than in plasma and significantly increased levels of fecal calprotectin (FC) were found in patients with bowel inflammation disease (IBD) [1]. It is noteworthy that FC is resistant to degradation and stable. The amount of FC is proportional to the amount of neutrophil migration into the gut lumen and can be used as a sensitive appropriate biomarker of gastrointestinal inflammation [6]. Fecal calprotectin is expected to support or replace histological assessment as a non-invasive biomarker because of its proven strong correlation with histological activity [1].

Hyperbaric oxygen therapy is a treatment in which patients breathe 100% oxygen while inside a hyperbaric chamber pressurized to greater than sea level. For clinical efficacy, pressures applied usually range from 2-3 atmosphere absolute (ATA), which is delivered in multiplace or monoplace chambers [7]. Hyperbaric oxygen therapy has potent anti-inflammatory effect and may normalize oxygen level in ischemic tissues [8].It increases the oxygen content of blood reaching inflamed bowel and alters signaling pathways involved in the tissue response to hypoxia and wound repair, notably hypoxia inducible factor (HIF) and heme-oxygenase pathways [9].

The aim of the present study was to evaluate the efficacy of hyperbaric oxygen as an adjuvant therapy in severe ulcerative colitis patients.

Subjects and Methods

Experimental Design

This study was conducted on 20 random Egyptian patients aged ≥18years who had severe UC flare according to truelove and Witt's criteria and admitted to gastroenterology department at Air force general hospital for 14 days then divided into two groups:

- Group I: composed of 10 patients managed by 10 sessions of HBO in multiplace chamber each session lasted 60 minutes with a 5 minutes break at 30 minutes to minimize risks for CNS toxicity at pressure depth 2.8 ATA five times per week for two consecutive weeks plus 400 mg hydrocortisone IV daily and IV fluids.

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- Group II: composed of 10 patients managed by 400 mg hydrocortisone IV daily plus IV fluids.

Inclusion Criteria

- Both gender included.
- Age ≥18years old.
- Severe UC characterized by presence of >6 bloody stools/day along with any one of the following: tachycardia > 90 beat per minute, fever > 37.8°C hemoglobin <10.5 gm/dL, and/or ESR >30 mm/hour (Truelove and Witt's criteria).

Exclusion Criteria

- History of barotrauma.
- Patients with>6 motions per day or CRP > 45mg/dL for rescue therapy with ciclosporin or biological therapy.
- Hepatitis B, C and tuberculosis patients.
- Upper respiratory tract infections.
- Mild and moderate UC patients.
- Congestive heart failure patients.
- Chronic obstructive pulmonary disease patients.
- Claustrophobia.
- Pregnant ladies.
- Recent surgeries.
- Patients who refused to be entitled in the study.

Ethical Considerations

This study was approved by Research Ethics Committee (REC) of Faculty of Medicine Ain Shams University (FMASU) according to the specific national laws where applicable (FMASU M D 181/2018). All methods were performed in accordance with the relevant guidelines and regulations. All participants did not expose to any risk or complications and a written informed consent was taken from all patients before participating in the study.

Study Procedures

All participants were subjected to history taking, clinical examinations, Abdominal x-ray on admission to exclude toxic megacolon, laboratory investigations as stool analysis to exclude other causes of bloody diarrhoea.

We used Mayo scoring system **Table (1)** for assessment of UC severity and the efficacy of therapeutic strategy for both groups in this study. It is composed of the rectal bleeding score (RBS), stool frequency score (SFS), endoscopic sub-scores (MES) and physician global score to formulate the score which ranges from 0 to 12, with higher scores indicates disease severity. We used only the first 3 components of Mayo score (RBS, SFS and MES) and didn't use physician global score as it's a subjective one. We calculated RBS and SFS at day 1, day 7 and day 14 of

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the study to detect disease severity before treatment and assess patient's response to the therapeutic strategy in both groups. Patients of both groups underwent colonoscopy at day 14 of the study (**Model: Fujifilm EC-590WL4)** to calculate their MES.

Table 1. Mayo scoring system for UC severity

Mayo index	0	1	2	3
Stool frequency	Normal	1-2/day more than normal	3-4/day more than normal	>4/day more than normal
Rectal bleeding	None	Visible blood with stool<half the time	Visible blood with stool half of the time or more	Passing blood alone
Mucosa	Normal	Mild friability, decreased vascular pattern	Moderate friability, erosions	Spontaneous bleeding, ulcerations
Physician global assessment	Normal	Mild	Moderate	Severe

Hyperbaric chamber
Patients received HBOT at hyperbaric unit located at Air-forces general hospital, Cairo, Egypt in a multiplace chamber (Model: HAUX-STARMED 2300).

Colonoscopy
Patients of both groups underwent colonoscopy (Model: Fujifilm EC-590WL4) at day 14 of the study to calculate their MES.

Sample collection
Five ml venous blood samples were drawn under complete aseptic conditions and were used to measure various laboratory parameters as complete blood count (CBC), liver and renal profile plus inflammatory markers as erythrocyte sedimentation rate and C-reactive protein which determined by routine laboratory analysis within three days prior to or following collection of the stool sample used for calprotectin measurement.

Collection of stool sample.
The stool samples were collected on the day of colonoscopy, or a few days prior to colonoscopy and stored in a refrigerator until the day of the colonoscopy. Upon receipt in the laboratory, all stool samples were registered and stored at -20˚C. Following thawing, the fecal samples were prepared and analyzed according to the test manufacturer's protocol.

Biochemical Analysis

Determination of inflammatory markers
A blood sample was also obtained from each patient to measure CRP was measured by Auto Analyzer (Hitachi Co. Japan) according to kit's instruction manual (Bionic Co.) and ESR was

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measured by Westergren method within three days prior to or following collection of the stool sample used for calprotectin measurement [10].

Determination of fecal calprotectin

Fecal calprotectin was measured according to Oyaert et al. [11] using a quantitative enzyme-linked immunosorbent assay (ELISA) and following the kit's instructions.

Statistical Analysis

Data entry and statistical analysis by SPSS statistical software package (SPSS Inc., Chicago, IL). Chi-square test to compare the difference between 2 qualitative variables. Independent sample t-test to compare the significance of differences for parametric variable between 2 independent means. Paired samples t-tests for statistical significance assessment of sample of matched pairs of similar units or one group of units which tested twice.

Results

Table 2. Comparison between group I and group II regarding ESR level at day 1, day 3, day 7 and day 14 of the study

ESR		Group I No. = 10	Group II No. = 10	Test value•	P-value	Sig.
Day 1	***Mean ± SD***	39.10 ± 4.82	38.10 ± 5.13	-0.449	0.659	NS
	Range	32 – 46	31 – 47			
Day 3	***Mean ± SD***	31.30 ± 4.76	33.00 ± 4.83	0.793	0.438	NS
	Range	25 – 39	26 – 40			
Day 7	***Mean ± SD***	21.80 ± 4.26	27.70 ± 4.08	3.160	0.005	HS
	Range	16 – 28	22 – 36			
Day 14	***Mean ± SD***	12.30 ± 1.25	22.80 ± 2.97	10.291	0.000	HS
	Range	11 – 15	19 – 29			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

•: Independent t-test

Table (2) shows that there was no statistically significant difference between the two studied groups regarding mean ESR level at day 1 and day 3 with p-values=0.659 and 0.438 respectively, but shows that there was highly statistically significant difference between them at day 7 and day 14.

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Table 3. Comparison between group I and group II regarding CRP level at day 1, day 3, day 7 and day 14 of the study

CRP		Group I	Group II	Test value•	P-value	Sig.
		No. = 10	No. = 10			
Day 1	***Mean ± SD***	37.70 ± 5.52	37.80 ± 4.66	0.044	0.966	NS
	Range	31 – 48	31 – 45			
Day 3	***Mean ± SD***	30.10 ± 4.70	33.70 ± 4.00	1.844	0.082	NS
	Range	24 – 38	27 – 39			
Day 7	***Mean ± SD***	19.10 ± 2.77	27.80 ± 3.39	6.284	0.000	HS
	Range	16 – 24	21 – 33			
Day 14	***Mean ± SD***	12.90 ± 1.66	23.10 ± 2.64	10.327	0.000	HS
	Range	10 – 15	19 – 27			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: Independent t-test

Table(3) shows that there was no statistically significant difference between the two studied groups regarding mean CRP level at day 1 and day 3 with p-values=0.966 and 0.082 respectively but shows that there was highly statistically significant difference between them at day 7 and day 14.

Table 4. Comparison between group I and group II regarding faecal calprotectin level at day 1, day 7 and day 14 of the study

Faecal calprotectin		Group I	Group II	Test value•	P-value	Sig.
		No. = 10	No. = 10			
Day 1	***Mean ± SD***	653.60 ± 80.28	632.40 ± 92.43	-0.548	0.591	NS
	Range	534 – 765	521 – 788			
Day 7	***Mean ± SD***	479.50 ± 62.17	566.20 ± 88.25	2.540	0.021	S
	Range	410 – 578	460 – 710			
Day 14	***Mean ± SD***	288.00 ± 20.94	503.80 ± 77.81	8.469	0.000	HS
	Range	257 – 315	420 – 620			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
• Independent t-test

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Table (4) shows that there was no statistically significant difference between the two studied groups regarding mean faecal calprotectin level at day 1 with p-value=0.591 but shows that there was statistically significant difference between them at day 7 with p-value= 0.021 and highly statistically significant difference between the two groups at day 14.

Table 5. Comparison between group I and group II regarding RBS at day 1, day 7 and day 14 of the study

RBS		Group I No. = 10	Group II No. = 10	Test value≠	P-value	Sig.
Day 1	***Mean±SD***	2.30 ± 0.48	2.30 ± 0.48	0.000	1.000	NS
	Range	2 – 3	2 – 3			
Day 7	***Mean±SD***	1.30 ± 0.48	1.60 ± 0.52	-1.314	0.189	NS
	Range	1 – 2	1 – 2			
Day 14	***Mean±SD***	0.30 ± 0.48	1.30 ± 0.68	-2.924	0.003	HS
	Range	0 – 1	0 – 2			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
≠: Mann-Whitney test

Table (5) shows that there was no statistically significant difference between the two studied groups regarding mean RBS at day 1 and day 7 with p-values=1.000 and 0.189 respectively, but shows that there was highly statistically significant difference between them at day 14.

Table 6. Comparison between group I and group II regarding SFS at day 1, day 7 and day 14 of the study

SFS		Group I No. = 10	Group II No. = 10	Test value≠	P-value	Sig.
Day 1	***Mean±SD***	2.40 ± 0.52	2.50 ± 0.53	-0.438	0.661	NS
	Range	2 – 3	2 – 3			
Day 7	***Mean±SD***	1.40 ± 0.52	1.60 ± 0.52	-0.872	0.383	NS
	Range	1 – 2	1 –2			
Day 14	***Mean±SD***	0.30 ± 0.48	1.30 ± 0.68	-2.924	0.003	HS
	Range	0 – 1	0 – 2			

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P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
≠: Mann-Whitney test

Table (6) shows that there was no statistically significant difference between the two studied groups regarding mean SFS at day 1 and day 7 with p-values=0.0661 and 0.383 respectively, but shows that there was highly statistically significant difference between them at day 14.

Table 7. Comparison between group I and group II regarding MES at day 14 of the study

MES	Group I	Group II	Test value	P-value	Sig.
	No. = 10	No. = 10			
Mean±SD	1.00 ± 0.67	1.60 ± 0.52	2.013≠	0.044	S
Range	0 – 2	1 – 2			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
≠: Mann-Whitney test

Table (7) shows that there was statistically significant difference between the two studied groups regarding mean MES at day 14.

Discussion

Ulcerative colitis is a chronic relapsing disease that involves the colorectal mucosa. Over the years, the therapeutic target has been upgraded from the resolution of symptoms to deep remission to prevent relapses and complications. So our goal in this study was to evaluate the hyperbaric oxygen as an adjuvant therapy in severe UC patients.

In our study we used Mayo scoring system Table (1) for assessment of UC severity and the efficacy of therapeutic strategy for both groups. It is composed of RBS, SFS, MES and physician global score to formulate the score which ranges from 0 to 12, with higher scores indicates disease severity. We used the first 3 components of Mayo score (RBS, SFS and MES) and didn't use physician global score as it's a subjective one. We calculated RBS and SFS at day 1, day 7 and day 14 of the study to detect disease severity before treatment and assess patient's response to the therapeutic strategy in both groups. Patients of both groups underwent colonoscopy at day 14 of the study to calculate their MES.

In this study we found that there was no statistically significant difference between the two studied groups regarding age with mean age of UC patients in group I was 25.7 vs 26.8 years in group II which is in agreement with **Esmat et al.,** [12].who stated that the mean age of diagnosis for UC patients residing in Cairo was 27.9 years, while the mean age for those living outside Cairo was 25.9 years. Recent European and Canadian data also observed a maximal incidence of UC in the 20–29 years age group.

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We found that there was marked significant reduction in inflammatory markers (ESR, CRP and faecal calprotectin) in group I in comparison to group II at the end of the study. Regarding ESR, we observed that there was no statistically significant difference between the two groups in mean ESR level at day 1 and day 3 (p-values=0.659 and 0.438) respectively, but we observed that there was highly statistically significant difference between them at day 7 and day 14 of the study (p-values=0.005 and 0.000) respectively with lower mean ESR level in group I in comparison to group II at day 3(31.30 ± 4.76 mm/h vs 33.00 ± 4.83 mm/h), day 7 (21.80 ± 4.26 mm/h vs 27.70 ± 4.08 mm/h) and day 14 of the study (12.30 ± 1.25 mm/h vs 22.80 ± 2.97 mm/h) as **Rossignol**. **[13]** stated that HBOT has been shown to possess potent anti-inflammatory properties and decrease the production of pro-inflammatory cytokines (TNF-alpha, interferon-gamma, Interleukin [IL]-1 and IL-6) as well as increase IL-10 levels and decrease inflammation by reduced tissue edema.

Regarding CRP, we observed that there was no statistically significant difference between the two groups regarding mean CRP level at day 1 and day 3 (p-values=0.966 and 0.082) respectively, but we observed that there was highly statistically significant difference between them at day 7 and day 14 of the study (p-values=0.000 and 0.000) with lower mean CRP level in group I in comparison to group II at day 3(30.10 ± 4.70 mg/dL vs 33.70 ± 4.00 mg/dL), day 7 (19.10 ± 2.77 mg/dL vs 27.80 ± 3.39 mg/dL) and day 14 of the study (12.90 ± 1.66 mg/dL vs 23.10 ± 2.64 mg/dL) in agreement with **Dulai et al.[**14]who found that a small but statistically significant reduction in CRP was also observed by day 3 with HBO (p-value=0.012, median reduction 7 mg/dL) and more reduction at day 5 during the study of the effect of HBOT on 18 patients with severe UC.

Eltzschig and Carmeliet. [15] justified the effect of HBO on patients of UC as their Gastrointestinal mucosa develops hypoxia which increase oxidative stress, inhibit mitochondrial function and increase inflammation leading to tissue oedema and impaired oxygen extraction from arterial supply to tissue and a vicious cycle between hypoxia and inflammation is seen which is abolished by HBOT sessions by inhibition of the expression of HIF and its target genes. HBO also ameliorate hypoxia and inflammation in individuals with UC by reducing tissue oedema. HBO promotes increments in plasmatic partial pressures of O2, thus enhancing tissue levels of oxygenation. Tissue hyperoxia increases the healing processes as it leads to vasoconstriction and decreased edema and also stimulates angiogenesis and proliferation of fibroblasts and collagen.

Faecal calprotectin data shown that there was statistically significant difference between the two groups at day 7 of the study (p-value=0.021) with mean faecal calprotectin level=479.50 ± 62.17 µg/mg in group I vs 566.20 ± 88.25 µg/mg in group II, but there was highly statistically significant difference between them at day 14 of the study (P=value =0.000) with lower mean faecal calprotectin level =288.00 ± 20.94 in group I vs 503.80 ± 77.81 µg/mg in group II as faecal calprotectin is considered a unique marker of IBD, **Mahdipoura et al**.,[16]stated that faecal calprotectin is known as the biomarker and the main actor of pathophysiological processes in UC which stimulates inflammatory response by increasing the production of certain inflammatory chemokines so their reduction in group I in comparison to group II indicates remission of the activity of UC flare and efficacy of HBOT.

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Dulai et al. [17] justified these results as the reactive oxygen and reactive nitrogen species generated by brief HBO exposures may function as intermediates in the nitric oxide synthase, and vascular endothelial growth factor (VEGF) signaling pathways. The net effect of these various influences could be blunting of the inflammatory cascade, inhibiting of immune cell responses and enhancing epithelial integrity, all of which may be responsible for the demonstrated efficacy of HBOT in UC.

Regarding RBS, we detected mean RBS at day 1= 2.30 ± 0.48 points in both groups but there was more reduction at day 7 of the study in group I> group II (1.30 ± 0.48 points vs 1.60 ± 0.52 points) but this result failed to get any statistically significant reduction between the two groups (p-value= 0.189). At day 14 of the study we observed that there was highly statistically significant reduction in mean RBS between the two groups (p-value=0.003) and mean RBS in group I= 0.30 ± 0.48 points vs 1.30 ± 0.68 points in group II.

Concerning SFS, we calculated it for both groups at day 1, day 7 and day 14 of the study, we found that there was no statistically significant difference between them at day 1 and day 7 with mean SFS in group I=2.40 ± 0.52 points at day 1 and 1.40 ± 0.52 points at day 7 vs 2.50 ± 0.53 points and 1.60 ± 0.52 points at day 1 and day 7 in group II respectively, but we found that there was highly statistically significant difference between them at day 14 (p-value= 0.003) as there was marked reduction in mean SFS at group I in comparison to group II (0.30 ± 0.48 points vs 1.30 ± 0.68 points).These results matching with **Dulai et al.** [14]who noted that among the 20 patients included in their trial who received HBOT plus steroids, 11 (55%) responded by day 3 based on the modified partial Mayo score (reduction in SFS + RBS of 2 or more points with at least a 1-point drop in RBS), HBO resulted in statistically significant reductions in the modified partial Mayo score by study day 3 (p-value < 0.001; mean change of 1.4 point), the RBS (p-value < 0.001; mean change of 1 point).

Dulai et al. [14] also noted that 6 patients achieved a RBS of 0-1by study day 5 and found that SFS specifically was also significantly lower (0.7 vs 2.6 points) in patients who received 5 HBOT sessions at day 10.

Finally, to calculate MES, patients from the two groups underwent colonoscopy at day 14 of the study after completion of HBO sessions and steroids therapy. We observed that there was statistically significant difference between them (p-value=0.044) (Table 1) and marked lower mean MES in group I in comparison to group II (1.00 ± 0.67 points vs 1.60 ± 0.52 points).

This marked reduction in all inflammatory markers in group I in comparison to group II is matching with **Bekheit et al.** [18]who justified these results as HBOT uses the concept of increased oxygen delivery to inflamed mucosa might reverse the tissue hypoxia that occurs in UC, stimulates colonic stem cells and induces mucosal healing. **Dulai et al.[**19] demonstrated that when HBOT was used alongside IV steroids for hospitalized UC patients suffering from acute flares, a significantly higher rate of clinical response and remission, and significantly lower rate of progression to second-line medical or surgical therapy was observed.

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Conclusion

We conclude that HBOT is a safe and a tolerated treatment option for severe UC patients beside conventional therapies to help avoid second-line therapies and surgical interventions. It uses the increase oxygen delivery to inflamed mucosa reversing the tissue hypoxia that occurs in UC, stimulates colonic stem cells, induces mucosal healing and suppresses the production of pro-inflammatory chemokines responsible for the metabolic stress created during active inflammation.

Declarations

Funding

Our research was funded totally by authors own money.

Conflicts of interest

There were no conflicts of interest regarding publication of our research.

Availability of data and material

All the data and material supporting the results of our research are included within the article.

Ethical Approval

This study was accepted by Ain Shams University Ethical Committee.

Informed consent

A written informed consent was taken from all patients before their participation.

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