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EFFICACY, SAFETY, AND TOLERABILITY EVALUATION OF GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING IRRITABLE BOWEL SYNDROME (CONSTIPATION – PREDOMINANT) (IBS–C)

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Data Requirement: Rome II Criteria for IBS

Guidelines Followed:

(i) Good Clinical Practice described under ICH E6 document

(ii) World Medical Association's Bioethics Declaration of Helsinki (as adopted by the WMA General Assembly, Tokyo, October 18, 2004) on ethical principles for Medical Research involving human subjects.

(iii) Schedule Y in Drugs and Cosmetic Act and Rules (2nd Amendment), 2005, Ministry of Health and Family Welfare, Government of India,

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ABSTRACT

An open, randomized, comparative, Phase II clinical trial on 20 patients with Constipation – Predominant Irritable Bowel Syndrome (IBS–C) was conducted for 6 weeks for evaluating safety, tolerability and efficacy of Oxy Powder® (OP) compared with Dulcolax (DX) tablets. The results indicated that complete cure was obtained in 30.8% and improvement in 69.2% patients treated with OP. In case of DX, improvement was seen in 71.4% patients and failure in 28.6% patients. There was no failure in case of OP indicating that efficacy of OP in treating IBS–C was significantly higher ($p<.05$) than DX.

KEYWORDS

GHC Oxy Powder®, Dietary supplement vs. Dulcolax– IBS–C Clinical Trial – Rome ll Criteria – ICH E6 GCP Guidelines– WMA Declaration of Helsinki – Drug Rules Schedule Y (Amendment 2005)

INTRODUCTION

Safety, tolerability and efficacy of Oxy Powder (OP) in treating chronic constipation have been described in Paper1. This paper deals with similar use of OP in treating **"**Irritable Bowel Syndrome (Constipation – Predominant) (IBS–C)". Irritable bowel syndrome (IBS) or spastic colon is a functional bowel disorder characterized by abdominal pain and changes in bowel habits which are not associated with any abnormalities seen on routine clinical testing. [1] IBS can be constipation-predominant (IBS-C), diarrhea-predominant (IBS-D) or alternate between constipation and diarrhea (IBS-A). Some times, IBS is "post-infectious IBS" (IBS-PI) which is Rome II criteria positive. For some people, however, IBS can be disabling but not fatal. The IBS-patients may be unable to work, attend social events, or even travel short distances. The symptoms, causes, diagnosis and treatment of IBS have been reported [2].

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Diagnosis of IBS – Rome II criteria for IBS

Irritable Bowel Syndrome can be diagnosed based on patient's symptoms during at least 12 weeks (which need not be consecutive) in the preceding 12 months, of *abdominal discomfort or pain that has two out of three of these features*:

1) Relieved with defecation; and/or, 2) Onset associated with a change in frequency of stool; and/or

3) Onset associated with a change in form (appearance) of stool.

Symptoms that Cumulatively Support the Diagnosis of IBS

1) Abnormal stool frequency (may be defined as greater than 3 bowel movements per day and less than 3 bowel movements per week); 2) Abnormal stool form (lumpy / hard or loose / watery stool);

3) Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation); 4) Passing of mucus in the faeces, 5) Bloating with abdominal distension.

Supportive Symptoms of IBS

1 Fewer than three bowel movements a week, 2 More than three bowel movements in a day

3 Passing hard or lumpy stools, 4 Loose (mushy) or watery stools, 5 Straining during a bowel movement, 6 Urgency (having to rush to have a bowel movement), 7 Feeling of incomplete bowel movement, 8 Passing mucus (white material) during bowel movement, 9 Abdominal fullness, bloating, or swelling

In this trial, every patient individually shall be evaluated for all the symptoms enumerated above.

Red Flag symptoms which are NOT typical of IBS

1) Pain that often awakens/interferes with sleep, 2) Diarrhoea that often awakens / interferes with sleep, 3) Blood in the stool (visible or occult), 4) Weight loss, 5) Fever, 6) Abnormal physical examination.

Diagnosis of IBS involves 'excluding conditions' which produce IBS-like symptoms ("Red flag" symptoms) and then following a procedure to categorize the patient's symptoms. Well-known algorithms include the Manning criteria, Kruise criteria, the Rome I and II criteria. [3, 4] They are useful for accurate diagnosis of IBS**.** Studies have compared their reliability [4] .The more recent Rome III Process was published in 2006 [5].

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The algorithm may include additional tests to guard against "Red flag" [6] symptoms which may include weight loss, GI bleeding, anemia, or nocturnal symptoms. There is no specific test for IBS, although diagnostic tests may be performed to rule out other problems. The diagnostic tests may include stool sample testing, blood tests, x-rays, colonoscopy / sigmoidoscopy [7]

No cure has been found for IBS; Tegaserod, a selective 5-HT4 agonist for IBS-C and Serotonin antagonists (Alosetron, a selective 5-HT3 antagonist for IBS-D) are used sometimes [7]. Colon cleansing achieved by 'Medical Ozone Oxygen therapy [8] through rectal insufflations is a natural alternative. Oxy Powder is an oral Dietary Supplement offering convenient alternative to otherwise painful 'Ozone Oxygen Therapy'. Each Oxy Powder capsule contains Ozonated Magnesium Oxide (OMO), Germanium Sesquioxide (Ge–132) and Natural Citric acid. OMO is presumed to release nascent oxygen in presence of Citric acid to give pH 4 in the G.I. tract. The magnesium assisted by (Ge-132) acts as a vehicle to transport oxygen throughout the body. Biochemical role of Ge-132 is reported by Sandra Goodman, [9] and others [10]. Germanium Sesquioxide has no known toxicities [11].

4 capsules of Test Product, Oxy Powder® "OP", with average weight of 715mg.are administered with water in the evening .The Reference Product, Dulcolax (Bisacodyl, DX) is a stimulant laxative. DX works by stimulating colon peristalsis. [12] DX is administered orally as a 5mg tablet with water at night

MATERIALS AND METHODS

(a) (i) Selection procedure of participants, patients 'Inclusion and Exclusion criteria', Pre–inclusion evaluation & documentation and Pre–study evaluation have been described in Paper – 1

(a) (ii) Participants Selected and basis:

Randomization:

The randomization of the patients was done as 2:1 i.e. out of 20 patients, 13 patients received OP (Group A) & 7 patients received DX (Group B).

Demography: Patients of both the sexes were included in the trial. In OP Group (Group A), out of 13 patients, 12 (92.3%) were males and 1 (7.7%) was a female while in DX Group (Group B), all 7 (100%) were

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males. The baseline demographic characteristics of patients were similar in two treatment Groups of the study (P> 05).

Living Habits– (a) Vegetarians / Non vegetarians (b) Smokers / Non smokers:

10 patients (76.9%) in Group A and 5 (71.4%) in Group B were Non vegetarians while 3 (23.1%) in Group A and 2 (28.6%) in Group B were vegetarians. 5 patients (38.5%) in Group A and none in Group B were smokers while 8 (61.5%) in Group A and 7 (100.0%) in Group B were Non smokers.

Categorization of Patients:

a) Duration of constipation in months:	3 – 12 months,	12 – 24 months,	> 24 months
Treatment Group A	3 (23.1%)	6 (46.2%)	4 (30.8%)
Treatment Group B	4 (57.1%)	2 (28.6%)	1(14.3%)

b) Number of bowels in a week:	1–4,	5–7,	8–14,	>14
Treatment Group A	1 (7.7%)	3 (23.1%)	6 (46.2%)	3 (23.1%)
Treatment Group B	0 (0.0%)	4 (57.1%)	2 (28.6%)	1 (14.3%)

c) Severity of Constipation:	Mild,	Moderate,	Severe
Treatment Group A	0 (0.0%)	11 (84.6%)	2 (15.4%)
Treatment Group B	0 (0.0%)	7 (100%)	0 (0.0%)

(b) Technical information

(i) Regulatory Approvals: Before commencing the studies, approval for the protocol was obtained from Independent Ethics Committee (IEC) of MCERC and of Bhatia Hospital, Mumbai.

(ii) Regulatory Guidelines followed: These included a) GCP guidelines described under ICH E6 document [13] b) World Medical Association's Declaration of Helsinki – 2004 [14] and Schedule Y in Drugs and Cosmetics Act (II Amendment) Rules, 2005, Ministry of Health and Family Welfare, Govt. of India [15]

(iii) Contributors, Investigator, Trial Center, No. of Patients Trial Duration and Details: (See Table 1)

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Table 1.

Trial Details

Investigator	Center	Treatment		Trial Duration
		1	2	
		Patients in OxypowderGr.	Patients in Dulcolax Gr.	
Dr. Chetan Bhatt	Bhatia Hospital	13	07	6 weeks

(A) Oxy powder (Marketed by Global Healing Center, Inc.; USA) **–Test Product A**

Each capsule contains 685 mg Ozonated Magnesium Oxides, 5.5 mg Ge–132 and 25 mg Natural Citric acid encapsulated in Kosher certified "00" vegetarian capsules

(B) Dulcolax Tablets (5mg/tablet), [manufactured by Zydus Cadila Ltd., (India)]**–Comparative Reference Product B**.

Each tablet contained Bisacodyl 5 mg (One tablet was encapsulated in '00' size opaque, white, empty hard gelatin capsule to match the size and color of OP capsule for administration to patients in DX group).

(d) Handling and Storage of Investigational Products:

Method described in Paper1 was followed.

Methods:

Dosage & Administration:

Selected patients were divided in two treatment Groups; Patients in Group 1 (OP) (assigned 13 patients) were administered Product A while Patients in Group 2 (DX) (assigned 7 patients) were administered Product B.

Test Product Oxy Powder (OP) (A):

The dose used for Cleansing Procedure, the Maintenance Dose and the procedures employed were same as are described in Paper 1

Comparative Product Dulcolax (DX) (B):

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DX administration procedure followed was same as "directed by the investigators" and described in Paper 1.

Drug Accountability and Patient monitoring: This was achieved during 'Patient monitoring' by instructing them to record the date and the time of taking dose at home in a formatted diary supplied to them. (See Paper 1)

Study Evaluation and Monitoring end points:

Efficacy: a) Findings of (i) Stool examination (ii) Barium meal X-Ray and (iii) Colonoscopy

(b) Relief of Constipation

The evaluated parameters recorded in 'OP– administered patients' were compared with those obtained in 'DX – administered patients.

Safety: During conduct of study, patients were continuously monitored for any side effects, ADRs and SAEs

Tolerability: During entire tenure of the study, all the patients were asked whether they experienced any discomfort.

Grading of Response:

Efficacy:

a) Overall therapeutic response was graded individually by the investigator with each patient as 'Excellent', 'Good', 'Fair' & 'Poor'. It was also simultaneously graded independently by Patients using same scale.

b) Therapeutic efficacy was correlated and graded as 'Complete Cure', 'Improvement' and 'Failure'.

Safety: Severity of each Adverse Event was proposedly rated as 'Mild' (no limitation of usual activity), 'Moderate' (some limitation of usual activity), and 'Severe' (inability to carry out usual activities).

Withdrawal from Study: All 20 enrolled patients completed the trial.

RESULTS

Study Medication and Efficacy evaluation.

(a) Record of Weight Variation: All the patients were checked for their weight every day for 0 to 6 days & then on day 21 & day 42. Mean weight during this period ranged from maximum 65.19 (± Mean SD 12.670) (day 0) to minimum 64.96 (± Mean SD 12.820) kg for patients in Group A and 64.00 (± Mean SD 11.255) (day 0) to minimum 63.19 (± Mean SD 11.640) kg for patients in Group B. The minor weight loss started from day 2 onwards in case of both treatments.

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RESPONSE OF PATIENTS TO THE TREATMENT OF SYMPTOMS AS PER ROME II DIAGNOSTIC CRITERIA FOR IBS [6] IN "TREATMENT GROUPS A AND B" ON DAY 0, 21 AND 42

(b) Record of No. of bowels passed by patients in a Week (Results are shown in Table 2)

Table 2

Average Number of Bowels passed in a week (Grouped)

No. Of Bowels	Day 0		Day 21		Day 42	
	Patients in treatment Gr.		Patients in treatment Gr.		Patients in treatment Gr.	
	A	B	A	B	A	B
1 – 4	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
5 – 7	3 (23.1%)	4 (57.1%)	2 (15.4%)	2 (28.6%)	1 (7.7%)	2 (28.6%)
8 –14	6 (46.2%)	2 (28.6%)	8 (61.5%)	4 (57.1%)	11 (84.6%)	5 (71.4%)
> 14	3 (23.1%)	1 (14.3%)	3 (23.1%)	1 (14.3%)	1 (7.7%)	0 (0%)
Total	13 (100%)	7 (100%)	13 (100%)	7 (100%)	13 (100%)	7 (100%)

IN GENERAL, NO. OF PATIENTS

(c) Who experienced Straining during >25% of Bowel Movement decreased from

13 (100.0%) on day 0 through 6 (46.2%) on day 21 and 1(7.7%) on day 42 in Group A

07 (100.0%) on day 0 through 4 (57.1%) on day 21 and 1(14.3%) on day 42 in Group B

(d) Passing Lumpy Stools reduced from

12 (92.3%) on day 0 through none (0.0%) on days 21 and 42 in Group A

6 (85.7%) on day 0 through 2(28.6%) on day 21 and 1 (14.3%) on day 42 in Group B

(e) Who experienced Sensation of incomplete evacuation for >25% of Bowel movement reduced from

13 (100.0%) on day 0 through 11(84.8%) on day 21 and 3 (23.1%) on day 42 in Group A

07 (100.0%) on day 0 through 5 (71.4%) on day 21 and 3 (42.9%) on day 42 in Group B

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(f) Who experienced Sensation of Anorectal Blockage for >25% of Bowel Movement reduced from 5 (38.5%) on day 0 to none thereafter in Group A

4 (57.1%) on day 0, 1 (14.3%) on day 21 and none on day 42 in Group B

(g) Who resorted to Manual Maneuvers to facilitate >25% of Bowel Movements

Reduced from 4 (30.8%) on day 0 to none thereafter in Group A

None of the patients resorted to manual maneuvers on days 0, 21and 42 in Group B

h) Who experienced relief in Abdominal Pain with defecation?

Reduced from 10 (76.9%) on day 0 to all 13 (100.0%) on days 21 and 42 **i**n Group A

All 7 patients got relief in abdominal pain with defecation on days 0, 21 and 42 in Group B

i) Who experienced change in Abdominal Pain onset with a change in frequency of stools increased from

3 (23.9%) on day 0 through 11(84.6%) on day 21and 13(100.0%) on day 42 in Group A

2 (28.6%) on day 0 through 7(100.0%) on days 21 and 42 in Group B

j) Who experienced change in Abdominal Pain onset with a change in the form of stools decreased from

7 (53.8%) on day 0 through 1(7.7%) on day 21 to none (0.0%) on day 42 in Group A

5 (71.4%) on day 0 through 1(14.3%) on days 21 and 42 in Group B

k) Passing mucus during bowel movement changed from

3 (23.1%) on day 0 to none on days 21 and 42 in Group A

2 (28.6%) on day 0 through none (0.0%) on day 21 to 1(14.3%) on day 42 in Group B

l) Who experienced abdominal fullness decreased from

11 (84.6%) on day 0 through 4 (30.8%) on day 21 to 1 (7.7%) on day 42 in Group A

7 (100.0%) on day 0 to 1(14.3%) on days 21 and 42 in Group B

Summary of Judgment on Efficacy independently given by (a) Investigator and (b) Patients.

Group A, (out of 13)

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IA* – Excellent for 6 (46.2%), Good for 5 (38.5%), Fair for 2 (15.4%),

PA –** Excellent for none (00.0%), Good for 7 (53.9%), Fair for 6 (46.1%),

Group B, (out of 07)

IA – Excellent for none (00.0%), Good for 3 (42.9%), Fair for 2 (28.6%), Poor for 2 (28.6%)

PA – Excellent for none (00.0%), Good for 3 (42.9%), Fair for 3 (42.9%), Poor for 1 (15.4%)

Overall efficacy adjudged by investigator was described as complete cure, Improvement and Failure.

Group A, (out of 13), **IA–** Complete cure, 4 (30.8%), Improvement, 9 (69.2%), failure, none (00.0%)

Group B, (out of 07), **IA–** Complete cure, none (00.0%), Improvement, 5 (71.4%), failure, 2 (28.6%)

Note: [IA* = Investigators' Assessment and PA** = Patient's Assessment (P< 0, 05),

Results were statistically analyzed using Fisher's Exact Test.

SAFETY:

None of the patients either in Group1 or in Group 2 experienced any adverse events during the study period.

DISCUSSION

According to Rome II criteria for constipation, all the patients included were sufferings from constipation for 12 weeks or more. They were suitably assigned to Groups for meaningful conduct of the trial.

- The baseline demographic characteristics of patients were similar in the two treatment Groups of the study (P>.05).
- Changes in weight during 42 days treatment in both the Groups were insignificant.
- All 20 patients had normal Barium meal X-ray and colonoscopy before starting with the treatment.

During the course of study, 5 patients among those having multiple spasmodic contractions in sigmoid and descending colon with impacted fecal matter and randomly selected from both Groups showed no differences in colonoscopy and Barium meal X-ray conducted on days 0, 21 and 42

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- (No organic lesions). Since no significant differences were observed, it was decided to drop conduct of both these tests on day 42. However, the patients continued with these two tests on day 0.
- Routine stool examination done on days 0 and 42 did not show any abnormality in all 20 patients included in this study.
- Analysis of oxygen content on days 0, 21and 42 showed marginal changes as compared to the baseline values
- During course of the study, patients in both Groups showed significant reduction in various symptoms typical of IBS.

CONCLUSIONS

(i) Efficacy assessment done independently by (a) the investigator and (b) the patients indicated that Efficacy of Oxy Powder in treating Irritable Bowel Syndrome (IBS–C) was significantly higher ($P<.05$) than Dulcolax indicating that Oxy Powder was more efficacious in treating (IBS–C) than Dulcolax.

(ii) As regards Safety, there were no side effects, ADRs or SAEs associated with administration of Oxy Powder proving that the product was "Safe".

(iii) As regards Tolerability, Patients on Oxy Powder treatment showed Excellent Tolerability towards the product and wanted to continue using the product after completion of the course

Although, in this study, the side effects of Dulcolax did not precipitate, literature reports [12] have several of them recorded**.** In comparison, **Oxy Powder** has a better safety profile as there are no ADRs reported so far**.** **Oxy Powder** is well tolerated by the patients.

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CONFLICTS OF INTEREST NOTIFICATION PAGE

(A) Individual Authors' Commitments

(B) Project Support (Financial Disclosure – DISCLAIMER) for Publication Paper 1: Evaluation of Safety, Tolerability and Efficacy of Oxy-Powder in Treating Chronic Constipation and Publication Paper 2: Safety, Tolerability and Efficacy of Oxy powder in treating IBS-associated with or without Constipation in Phase II Clinical trial (Published Separate) authored by

1) Prof. Jogender K. Lalla, the Main author,

2) Dr.Meena U. Shah, MBBS, MD, Co–author,

3) Dr.Deven Parmar, MBBS, MD, Co–author,

4) Dr.Edward F. Group III, DC, ND, DACBN,

Co–author, hereby state as follows:

- Author at Sr.No. 1, Prof. Jogender K. Lalla, B.Pharm, PhD, Study Director of the Contract Clinical Trial Project and Executive Director+ President of Mayfair Clinical, Education & Research Center (MCERC) (INDIA), a contract CRO,
- Author at Sr.No.2, Dr.Meena U. Shah, MBBS, MD., Study Monitor, QA Director and Clinical Pharmacologist of the Contract Clinical Trial project
- Author at Sr.No. 3, Dr.Deven Parmar, MBBS, MD, Study Coordinator of the Contract Clinical Trial project represent MCERC in the capacity enunciated above and are not connected to Global Healing Centre, USA in any manner financially except for the payment received from GHC towards conduct of Clinical Trial by MCERC and the payments made there from to investigators and other parties associated with conduct of this trial.

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➢ Author at Sr.No. 4, Dr. Edward F. Group III, DC, ND, DACBN, CEO of GLOBAL HEALING CENTER INC. (GHC), USA, Project Sponsor, Study Advisor and Monitor of GHC, does not have any financial stake or interest in MCERC except and only for the business deal in terms of the above clinical trial

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