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Original Article

An Exploratory Study on Integrative Management of Irritable Bowel Syndrome with Constipation (IBS-C)

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ABSTRACT

Irritable Bowel Syndrome (IBS) was complicated disorder that results in pain and change in bowel habits. The major contributing factors to the onset and detoriation include stress and gastrointestinal problem. The women between 20 to 40 years were most commonly involved. The prevalence varies among countries that was affected by diet and diagnostic criteria. **Objective:** Compairing the efficacy of Mebeverine, Polyethylene Glycol with the combination therapy of Mebeverine and Polyethylene Glycol in Irritable Bowel Syndrome associated with Constipation. **Methods:** The comparative analytical study was conducted at the National Medical Centre, Karachi, and approved by the Ethical Review Committee of Bahria University Health Science Campus. Participants aged 15-50 with IBS were selected to reflect the target population. Observational data were collected based on the treatments they naturally received: Mebeverine, Polyethylene glycol, or a combination. Pain and constipation status were recorded at baseline (day 0) and after 24 days, analyzing the effectiveness of the treatments as they were administered in routine care settings. **Results:** The demographic data mentioned comparable age, weight, height, and gender distribution across the three groups. Constipation and pain status before and after varied considerably across the investigation time. There was substantial improvements by day 24 from the baseline in the combination therapy. **Conclusions:** The combination of Mebeverine and Polyethylene glycol reveals in managing IBS, with prominent improvements in constipation severity over the research duration. This highlights the importance of multimodal treatment methods in addressing the varied symptoms of IBS and enhancing the quality of life.

INTRODUCTION

Irritable Bowel Syndrome (IBS) is a complicated condition involving the intestines. It is defined by changes in bowel habits and associated pain that is disturbing everyday life and ability to work normally . Multiple factors were involved that contribute to the onset of IBS, including impaired gastrointestinal movement, excessive bacterial presence, visceral sensitivity, changes in gut microbiota, impaired nutrient absorption, and inflammation [2]. Moreover, psychological factors like stress might worsen the severity of IBS symptoms [3]. This disorder normally affects more women than men, with onset frequently occurring between ages 20 and 29 years [4, 5]. The prevalence of irritable bowel syndrome (IBS) differs considerably between countries due to differences in dietary patterns, cultural influences, and diagnostic methodologies. Globally, the occurrence of IBS differs, influenced in part by the diagnostic criteria applied [6]. A meta-analysis mentioned 57 eligible studies, IBS prevalence was 9.2% using Rome III criteria and 3.8% with Rome IV criteria. IBS with mixed bowel habits was most common with Rome III, while IBS with diarrhea was most common with Rome IV. The prevalence of IBS was higher in women, and significant variability in prevalence was observed between countries, suggesting Rome IV criteria may be less suitable for broad

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epidemiological surveys [4]. While the nationwide prevalence of irritable bowel syndrome (IBS) in Pakistan is still unknown, a study conducted in the outpatient departments of internal medicine units at tertiary care hospitals across various cities found the prevalence of IBS in the general population to be 33.2% [7]. The categorization of lirrtable Bowel Syndrome (IBS) is based on stool pattern, distinguishing between diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed (IBS-M), or undefined (IBS-U) [8]. This syndrome significantly impacts sufferers' professional and social lives, often leading to a notable decline in quality of life (QoL). This condition can cause debilitating symptoms such as abdominal pain, bloating, and altered bowel habits, which frequently hinder daily activities and social interactions. Studies indicate that patients with IBS may experience anxiety, depression, and social withdrawal due to the unpredictability and discomfort associated with their symptoms [9]. The pathophysiology of irritable bowel syndrome (IBS) is multifaceted and increasingly recognized as involving various biological and psychosocial factors rather than being purely psychological. Key contributors include genetic predispositions, environmental influences, and gut-specific disturbances. The condition is characterized by visceral hypersensitivity, leading to heightened pain perception, as well as motility issues that can result in symptoms like abdominal discomfort, diarrhea, or constipation [10]. Recognizing IBS as a spectrum disorder with overlapping features suggests a comprehensive approach to diagnosis and treatment, taking into account genetic predisposition, dietary factors, gut microbiota, and dysfunction in the gut-brain axis [2]. The management of Irritable Bowel Syndrome (IBS) has gained global attention due to the limited success of single-agent treatments. Treatment strategies for IBS-C may include both non-pharmacological and pharmacological interventions, tailored to individual symptoms. An evolving method includes combining pharmacological agents from diverse classes to widely address symptom [11]. This investigation aimed to integrate first line drug with agents from diverse classes, such as antispasmodics, to bridge this gap. Antispasmodics, such as Mebeverine, deliver a safe selection, regardless of the indistinct mechanism of action. Mebeverine's numerous actions, as well as reducing ion permeability and blocking noradrenaline reuptake, contribute to its efficacy in managing IBS-related abdominal distress. It acts by relaxing gut muscles, making it a chosen treatment for IBS patients with major pain, as per present strategies [12]. Polyethylene Glycol (PEG), or macrogol, is a non-absorbable polymer marginally absorbed in the gastrointestinal tract. Large daily doses of PEG solution have revealed effectiveness in the management of fecal impaction and severe constipation. As an osmotic laxative, PEG's efficiency differs with dosage, with low adverse effects and increase tolerability. Its inert nature approves marginal impact on the movement of other substances in the gastrointestinal tract [13].

The aim of this study was to investigate the efficacy of combining Mebeverine and Polyethylene glycol in managing symptoms of irritable bowel syndrome with constipation (IBS-C) over a 24-day period, compared to monotherapy with either medication alone.

METHODS

This comparative analytical study was conducted as part of MPhil research at Bahria University Health Science Campus. Ethical approval was granted by the Ethical Review Committee of Bahria University Health Science Campus (Ref No: FRC/BUMD 14/2021-Pharm-108, ERC 81/2021). The study took place at the National Medical Centre in Karachi from December 2021 to June 2022, with consent obtained from the director and head of the institution. Participants aged 15-50 years were recruited and randomly assigned to one of three groups. Informed consent was obtained in both Urdu and English. A total of 162 participants completed the study, with assessments conducted at baseline (day 0) and after 24 days [14]. Based on the calculations, the total sample size of 162 participants was required, with an equal number of exposed and unexposed individuals to achieve 80% power at a 95% confidence level. The study included patients with type 1 and type 2 constipation, identified using the Bristol Stool Chart, who reported mild to severe pain according to the Visual Analog Scale. Participants of any gender or ethnicity who consented to the study were eligible. Prior to enrollment, participants underwent evaluations including medical history, physical examination, hematological tests, stool analysis, and blood tests for glucose and thyroid profiles. Exclusion criteria included previous use of any relevant treatments or interventions, as well as the presence of co-morbid conditions such as coronary artery disease, cardiac failure, chronic obstructive pulmonary disease, hypothyroidism, gluten hypersensitivity, diabetes, or malignancy. Data collection involved assessing participants' symptoms and responses through questionnaires at baseline and after 24 days. Group I received oral Mebeverine 135 mg twice daily, Group II received Polyethylene glycol 3350 once daily, and Group III received both treatments. Data from the questionnaires were entered into Microsoft Excel for descriptive analysis and analyzed using SPSS version 25.0. Descriptive statistics included mean, standard deviation, frequencies, and proportions. One-way ANOVA was used for numerical data, while Pearson's Chi-square tests were applied to categorical data. Reliability analysis using Cronbach's alpha showed high internal consistency for the constipation scale ($\alpha = 0.883$).

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RESULTS

In the study, a total of 162 patients suffering from irritable bowel syndrome (IBS) were surveyed. The demographic characteristics of patients across the three treatment groups (Groups I, II, and III) were comparable, as indicated by mean age, weight, height, and gender distribution. There were no statistically significant differences observed among the groups for age (p = 0.168), weight (p = 0.348), height (p = 0.795), or gender distribution (p = 0.974) as demonstrated in Table 1.

Table 1: Demographics of Patients in Groups I, II and III

Variables	Group I Mean ± SD / N (%)	Group II Mean ± SD / N (%)	Group III Mean ± SD / N (%)	p-Value
Age (Years)	30.28 ± 10.31	33.89 ± 9.91	32.56 ± 9.74	0.168[a]
Weight (Kg)	70.85 ± 12.90	67.56 ± 10.11	68.57 ± 12.86	0.348[a]
Height (m)	1.62 ± 0.10	1.62 ± 0.11	1.63 ± 0.11	0.795[a]
Gender				
Female	33 (61.1%)	34 (63.0%)	33 (61.1%)	0.974[a]
Male	21 (38.9%)	20 (37.0%)	21 (38.9%)	

Group I – recieved Mebeverine, Group II – received Polyethylene glycol, Group III – received Mebeverine + Polyethylene glycol δ
Age, Height and Weight One-way ANOVA,
Gender – chi square test
[a] – non-significant p-value > 0.05

In table 2 at day 0, a considerable proportion of patients in all three groups experienced severe constipation, ranging from 66.7% to 72.2%. However, there were no significant differences observed among the groups regarding the severity of constipation at baseline (p = 0.815). On the 24th day, constipation showed varying degrees of improvement across the three groups. In Group I, constipation remained unchanged in 21 (38.9%) participants, while in Group II, only 1 (1.9%) participant experienced no change, and in Group III, none reported unchanged constipation. Moderately relieved constipation was observed in 30 (55.6%) participants in Group I, 21 (38.9%) in Group II, and 4 (7.4%) in Group III. Significantly relieved constipation was reported by 3 (5.6%) participants in Group I, 32 (59.3%) in Group II, and 50 (92.6%) in Group III. These differences in constipation status on the 24th day were statistically significant across the three groups (p < 0.001).

Table 2: Constipation Status at Days 0 and 24 in IBS Patients

Variables	Group I N (%)	Group II N (%)	Group III N (%)	p-Value
Constipation (Day 0)				
Mild	18 (33.3%)	16 (29.6%)	15 (27.8%)	0.815[a]
Severe	36 (66.7%)	38 (70.4%)	39 (72.2%)	
Constipation (Day 24)				
Unchanged	21 (38.9%)	1 (1.9%)	0 (0.0%)	<0.001**
Moderately Relieved	30 (55.6%)	21 (38.9%)	4 (7.4%)	
Significantly Relieved	3 (5.6%)	32 (59.3%)	50 (92.6%)	

Group I – recieved Mebeverine, Group II – received Polyethylene glycol, Group III – received Mebeverine + Polyethylene glycol δ
Chi square test
[a] – non-significant p-value > 0.05, * – significant p-value < 0.05

In table 3, at day 0, the distribution of pain severity, as assessed by the Visual Analogue Scale (VAS), showed similar patterns across all three groups. The majority of patients reported moderate to severe pain, with proportions ranging from 53.7% to 70.4%. However, there were no significant differences observed among the groups regarding pain severity at baseline (p = 0.781). On day 24, there were notable changes in pain severity across the groups. In Group I, a considerable proportion of patients reported no pain (57.4%), while in Group II, fewer patients reported no pain (11.1%). Interestingly, in Group III, the vast majority of patients (87.0%) reported no pain. Conversely, the proportion of patients reporting severe pain decreased significantly in all groups, with the most substantial reduction observed in Group III. These differences in pain severity on day 24 were statistically significant across the three groups (p < 0.001).

Table 3: Pain Severity on Visual Analogue Scale (VAS) at Day 0 and Day 24 in IBS-C Patients

Variables	Group I N (%)	Group II N (%)	Group III N (%)	p-Value
VAS Day 0				
No Pain	2 (3.7%)	2 (3.7%)	2 (3.7%)	0.781[a]
Slight	13 (24.1%)	11 (20.4%)	8 (14.8%)	
Moderate	29 (53.7%)	26 (48.1%)	27 (50.0%)	
Severe	10 (18.5%)	15 (27.8%)	17 (31.5%)	
VAS Day 24				
No Pain	31 (57.4%)	6 (11.1%)	47 (87.0%)	<0.001*
Slight	23 (42.6%)	18 (33.3%)	7 (13.0%)	
Moderate	0 (0.0%)	29 (53.7%)	0 (0.0%)	
Severe	0 (0.0%)	1 (1.9%)	0 (0.0%)	

Group I – recieved Mebeverine, Group II – received Polyethylene glycol, Group III – received Mebeverine + Polyethylene glycol,
Chi square test
[a] – non-significant p-value > 0.05, * – significant p-value < 0.05

DISCUSSION

The investigation involved patients diagnosed with Irritable Bowel Syndrome (IBS) and concurrent constipation, between an age ranges from 15 to 50 years. This distribution of age in this study revealed a higher incidence of IBS among younger age groups with a mean age between 30 to 34 years. Similarly, a study conducted in Vietnam indicated a mean patient age of 36 years [15]. Particularly, investigation from Norway underscored a substantial occurrence of IBS among the younger population, with age below 40 years [16]. The greater incidence of Irritable Bowel Syndrome (IBS) among younger in this study and previous may be accredited to lifestyle stressors, dietary habits, and hormonal variations during adolescence and early adulthood. In this study, most of the participants (62%) were female, whereas 38% were male. Similar findings were witnessed in a European study, where 62% were female [17]. Moreover, investigation in Saudi Arabia

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revealed a higher prevalence of IBS among females, however the exact reason for this gender difference remains indistinct [18]. The current study showed the effectiveness of Mebeverine, Polyethylene glycol, and their combination in treating IBS symptoms over 24 days was assessed. Patients were grouped based on their natural treatment regimens: Mebeverine alone, Polyethylene glycol alone, or a combination of both. At the end of the 24-day period, significant improvement in pain severity, as measured by the Visual Analog Scale (VAS), was observed primarily in the group receiving combination therapy. This finding suggests that while each treatment individually had an impact, the combined approach may offer enhanced relief for IBS symptoms in a real-world clinical setting. A study conducted with 200 IBS patients, the effects of Mebeverine in pain management was evaluated. While pain scores showed no change at baseline, a notable decrease was observed by day 28 in the Mebeverine group. Additionally, PAC-QOL scores improved significantly from 91.54% to 53.52% by day 28 [19]. However, antispasmodics, a diverse medication class with various mechanisms, require comprehensive investigation for reliable recommendations. Despite its common prescription for IBS patients, meta-analyses in 2010 and 2012 found no clear effectiveness of mebeverine, contrasting with cumin sofouf, which showed statistically superior results in reducing IBS symptoms [20]. Moreover, a meta-analysis examined the effectiveness of Mebeverine in managing multiple symptoms associated with Irritable Bowel Syndrome (IBS). Incorporating twenty-two studies and approximately 1052 participants, the analysis revealed a significant reduction in pain (P-values ranging from <0.05 to <0.001), consistent with this study findings [12]. Another comparable study conducted at Tanta University's Gastroenterology Department involved 50 outpatients divided into two groups: one receiving Mebeverine alone and the other Mebeverine combined with Pentoxifylline. Both groups showed a significant decrease in Numeric Pain Rating Scale scores (P<0.0001) after three months. Contradictory to this findings, another study in India assessing the efficacy of 200mg controlled release Mebeverine revealed non-significant results (P-value 0.615). Despite expectations, this formulation did not alleviate severe symptoms, as indicated by bowel movement frequency, severity of abdominal cramps, and IBS quality of life score [21]. In this study, a notable proportion of patients across all groups experienced severe constipation at baseline, with no significant differences observed among them ($p = 0.815$). However, by the 24th day, significant improvements in constipation were evident in Group II and Group III exhibiting the most substantial relief compared to Groups I ($p < 0.001$). These findings highlight the efficacy of polyethylene glycol and combination therapy in alleviating constipation symptoms.

In Europe, Polyethylene glycol 3350 plus electrolytes (PEG3350+E) was the primary treatment for Chronic Constipation (CC), boasting superior efficacy and long-term tolerability compared to other laxatives [22]. A randomized clinical trial on children with functional constipation revealed significant stool consistency improvements with both single and divided doses of Polyethylene Glycol (PEG), corroborating this study's outcomes [23]. Furthermore, a meta-analysis emphasized the preference for Polyethylene Glycol (PEG) in irritable bowel syndrome with constipation (IBS-C) due to its favorable side effect profile and efficacy in reducing spontaneous bowel movements versus placebo, aligning with this study's findings on combination therapy efficacy [24]. The disparity in results between this adult-focused combination therapy study and the pediatric longitudinal study may be because of the differences in patient age, treatment protocols, and follow-up duration, indicating the need for tailored approaches in managing IBS across age groups. This study highlighted the complexity of treating Irritable Bowel Syndrome (IBS), underlining the effectiveness of combination therapies like Mebeverine and Polyethylene glycol in improving symptoms, particularly pain and constipation.

CONCLUSIONS

In conclusion, Mebeverine, Polyethylene glycol, and their combination therapy all showed positive results in managing IBS symptoms. Among these, combination therapy demonstrated the most promising outcomes, with notable improvements in symptom relief due to the synergistic effects of the combined treatments. The importance of personalized treatment approaches tailored to individual patient needs. Continued research was essential to refine therapeutic strategies and enhance outcomes for IBS patients, ultimately aiming to improve their quality of life through a better understanding of effective treatment modalities.

Authors Contribution

Conceptualization: ISR
Methodology: WY, MSAJ
Formal analysis: UZ
Writing, review and editing: SJI, SZ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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