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Efficacy of Bile Acid Sequestrants in Treating Bile Acid Diarrhea: A Double-Blind, Placebo-Controlled RCT

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Abstract

A double-blind, placebo-controlled randomized clinical trial evaluated the efficacy of colesevelam 1.875 g twice daily in adults with bile-acid diarrhea (BAD) confirmed by SeHCAT retention ≤10 %. Eighty participants were randomized (40 active, 40 placebo) and treated for 8 weeks. Baseline demographics and diarrhea severity were comparable between groups. Primary outcome was change in stools per day; secondary endpoints included stool consistency, urgency episodes, and quality of life (IBDQ-Short Form). At Week 8, the colesevelam group demonstrated a significant reduction in mean daily stools (from 5.4 ± 1.2 to 2.1 ± 0.9), compared with placebo (5.3 ± 1.1 to 4.8 ± 1.0; $p < 0.001$). Stool consistency improved (Bristol score reduction of 2.3 ± 0.7 vs. 0.4 ± 0.6; $p < 0.001$), as did urgency frequency (reduction 75 % vs. 10 %; $p < 0.001$). Quality-of-life scores increased by 21 % in the treatment arm versus 5 % with placebo ($p = 0.002$). No serious adverse events were reported; mild constipation occurred in 15 % of treated subjects. These results reveal that colesevelam significantly alleviates symptoms and enhances quality of life in BAD, marking a novel, large-scale confirmation in a rigorously controlled trial. Findings support adoption of colesevelam as a first-line targeted therapy in BAD. Key words: bile-acid diarrhea, colesevelam, randomized controlled trial.

Introduction

Bile acid diarrhea (BAD) constitutes a frequently underrecognized etiology of chronic watery diarrhea, presenting with high stool frequency, urgency, and decreased quality of life.^1 Its pathophysiology involves excessive spillover of bile acids into the colon—either through increased hepatic synthesis or impaired ileal reabsorption—stimulating secretion and motility.^2 The prevalence of BAD is estimated at around 1 % in the general population but is detected in 30–50 % of patients with chronic diarrhea or IBS-D, often misdiagnosed due to overlapping clinical features and limited diagnostic testing availability.^3,4 Early identification is paramount, as untreated BAD imposes substantial psychosocial and healthcare burdens.^5

The gold-standard SeHCAT retention test is inaccessible in many regions, prompting reliance on surrogate biomarkers (e.g., serum C4, FGF19) and empirical bile acid sequestrant (BAS) trials.^6,7 BAS such as cholestyramine, colestipol, and colesevelam reduce colonic bile acid contact by binding intraluminal bile acids, thereby normalizing stool frequency and consistency.^8 However, cholestyramine and colestipol suffer from poor palatability and tolerability, limiting adherence.^9 In contrast, colesevelam, a newer BAS with an improved side-effect profile, offers tablet-based dosing, enhancing ease of use and patient acceptance.^10

Early RCTs and observational studies demonstrated BAS efficacy in BAD, yet many lacked rigorous design or appropriately powered cohorts, and effects on patient-centered outcomes remained inadequately quantified.^11 Recent RCTs compare colesevelam to placebo and active comparators (e.g., GLP-1 agonist liraglutide), with promising but underpowered results.^12,13 Colesevelam has shown superiority to placebo in remission rates in BAD diagnosed biochemically (e.g., high serum C4), yet sample sizes and duration were limited.^13 Notably, head-to-head non-inferiority trials of colesevelam versus liraglutide highlight unique mechanistic differences between therapies but are yet to conclusively position colesevelam as first-line standard.^14

Mechanistically, colesevelam sequesters lumenal bile acids, increasing fecal excretion and reducing bile acid absorption. This reduces colonic irritation but triggers compensatory hepatic bile acid synthesis, reflected by increased serum C4 and decreased FGF19.^15 The impact of

colesevelam on gut microbiome composition remains under investigation; preliminary data suggest species-specific shifts without major diversity reduction.^12 Clarifying long-term effects on microbiota, transit, and patient-reported outcomes remains essential.

To further our understanding, large, double-blind, placebo-controlled trials are needed to establish colesevelam's efficacy and safety in a confirmed BAD cohort, with robust endpoints including stool frequency, consistency, urgency, quality of life, and biomarker correlates. Rigorous methodology, adequate sample size computation, and standardized outcome assessment would strengthen evidence and inform guideline recommendations. Moreover, elucidating tolerability and adverse event profile will support real-world applicability.

Given these gaps, the present study implemented an 8-week, double-blind, placebo-controlled RCT of colesevelam 1,875 mg BID in adults with BAD confirmed by SeHCAT retention ≤ 10 %. The trial evaluated daily stool frequency as the primary endpoint, with secondary outcomes assessing stool consistency (Bristol scale), urgency, and disease-specific quality of life. Safety monitoring included adverse events and routine labs. This trial represents one of the largest rigorously controlled studies of colesevelam with comprehensive symptom and biomarker outcomes, addressing long-standing gaps in evidence. The study offers novel insights into symptom relief and lays groundwork for BAS therapy optimization in BAD.

Methodology

This study was a prospective, double-blind, placebo-controlled randomized clinical trial conducted at a tertiary care gastroenterology center Nawaz Sharif Medical Colleg. Adults aged 18–65 years presenting with chronic watery diarrhea of at least six weeks' duration were screened. Diagnosis of bile acid diarrhea (BAD) was established by a SeHCAT retention scan showing <10 % retention at 7 days. Eligible participants provided verbal informed consent before randomization, as approved by the institutional review board (IRB/2023/GI/021). Ethical guidelines were adhered to per the Declaration of Helsinki.

Sample size was calculated using Epi Info™ version 7.2, with a power of 90 %, confidence level of 95 %, and a two-sided significance level of 0.05. Assuming a 30 % difference in symptom

resolution between colesevelam and placebo arms based on pilot data, and accounting for 10 % attrition, the total sample size was estimated at 80 participants (40 per group).

Inclusion criteria encompassed adults with SeHCAT-confirmed BAD, a minimum stool frequency of four per day, and stable medication use for the past 4 weeks. Exclusion criteria were inflammatory bowel disease, celiac disease, lactose intolerance, recent gastrointestinal surgery, malignancy, pregnancy, prior use of bile acid sequestrants within 3 months, and inability to provide consent. Participants with abnormal thyroid, liver, or renal function were also excluded to minimize confounding.

Randomization was performed using a computer-generated block design (block size 4) stratified by sex, to ensure balance across groups. Allocation concealment was achieved through sequentially numbered, opaque, sealed envelopes prepared by a third party. Investigators, participants, and data analysts remained blinded to group allocation.

Participants were assigned in a 1:1 ratio to receive either colesevelam hydrochloride 1.875 g twice daily or a matched placebo, orally, for 8 weeks. Compliance was monitored via tablet count and weekly follow-up calls. Adherence above 85 % was considered acceptable. Participants were advised to maintain a consistent diet and avoid new medications or probiotics throughout the study period.

The primary endpoint was change in daily stool frequency from baseline to week 8. Secondary endpoints included improvement in stool consistency based on the Bristol Stool Scale, frequency of urgency episodes per week, and quality of life measured via the validated IBDQ-Short Form questionnaire. Safety outcomes included adverse events, routine laboratory tests (complete blood count, liver function tests, renal profile), and gastrointestinal tolerability assessments.

Data were collected at baseline, week 4, and week 8. Clinical evaluations were conducted by blinded assessors. All adverse events were recorded and graded according to the CTCAE v5.0. Participants were allowed to withdraw at any time without penalty, and all data were anonymized for confidentiality. The trial was registered prior to initiation with the national clinical trials registry.

Results

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Colesevelam Group (n=40)	Placebo Group (n=40)	p-value
Age (years)	42.1 ± 10.5	41.3 ± 9.8	0.71
Male (%)	55%	52.5%	0.81
BMI (kg/m²)	25.6 ± 3.4	25.3 ± 3.1	0.67
Baseline SeHCAT Retention (%)	4.2 ± 1.1	4.3 ± 1.0	0.85
Duration of Diarrhea (months)	9.1 ± 2.3	9.3 ± 2.5	0.74

There were no significant baseline differences between the two groups, indicating successful randomization and group comparability.

Table 2. Clinical Outcomes at Week 8

Outcome	Baseline (Colesevelam)	Week 8 (Colesevelam)	Week 8 (Placebo)	p-value
Daily Stool Frequency	5.4 ± 1.2	2.1 ± 0.9	4.8 ± 1.0	<0.001
Bristol Stool Score	6.3 ± 0.5	4.0 ± 0.7	5.9 ± 0.6	<0.001
Urgency Episodes/Week	6.5 ± 1.8	1.6 ± 0.9	5.8 ± 1.5	<0.001
IBDQ-SF Score Improvement (%)	–	21 ± 5.6	5 ± 4.3	0.002

Colesevelam significantly improved all primary and secondary clinical outcomes compared to placebo, including stool frequency, urgency, consistency, and quality of life.

Table 3. Adverse Events During Study Period

Adverse Event	Colesevelam Group (n=40)	Placebo Group (n=40)	p-value
Constipation	6 (15%)	2 (5%)	0.04
Abdominal Bloating	3 (7.5%)	1 (2.5%)	0.30

Adverse Event	Colesevelam Group (n=40)	Placebo Group (n=40)	p-value
Nausea	2 (5%)	1 (2.5%)	0.55
Headache	1 (2.5%)	0	0.31
Serious Adverse Events	0	0	–

Adverse events were mild and more frequent in the colesevelam group, particularly constipation, but no serious adverse events were observed in either arm.

Discussion

This double-blind, placebo-controlled trial confirms the therapeutic efficacy of colesevelam in patients with SeHCAT-confirmed bile acid diarrhea, demonstrating statistically significant improvements across all key clinical endpoints, including stool frequency, consistency, urgency, and quality of life. The magnitude of symptom relief observed—more than 60 % reduction in daily stool frequency and an over fourfold increase in disease-specific quality of life—represents a clinically meaningful benefit not only in numerical terms but in restoring patient functionality and comfort. These findings reinforce colesevelam's role as a first-line therapeutic option in objectively confirmed BAD, particularly in cases resistant to dietary or empirical antidiarrheal therapy.^16

Previous studies on bile acid sequestrants, including those comparing cholestyramine and colesevelam, were limited by open-label designs, small sample sizes, or heterogeneous diagnostic criteria.^17 Our study overcomes these limitations through rigorous blinding, adequate power, and SeHCAT-based inclusion—ensuring a biologically homogenous cohort with documented bile acid malabsorption. Furthermore, the intervention dose (1.875 g BID) and follow-up duration (8 weeks) align with pharmacodynamic expectations of BAS action, allowing a robust temporal association between treatment and outcomes.^18 This trial provides some of the most compelling evidence to date for the standardized use of colesevelam in BAD.

The significant improvement in Bristol stool scores and urgency episodes further underscores the physiological relevance of bile acid sequestration in mitigating colonic stimulation. It is well-established that excess bile acids reaching the colon stimulate cyclic AMP-dependent chloride

secretion and accelerate motility via enteric nervous system activation.^19 Colesevelam's ability to bind dihydroxy bile acids and reduce their irritant effect likely explains the rapid symptom control, consistent with mechanistic findings in recent functional imaging studies of colonic response to bile acid load.^20 Additionally, improvement in IBDQ scores confirms a patient-centered benefit, aligning with recent expert recommendations prioritizing subjective symptom relief in BAD management algorithms.^21

Interestingly, the incidence of constipation was modestly higher in the colesevelam group (15 % vs. 5 %), reflecting known class effects of BAS. However, these events were mild, self-limited, and did not necessitate discontinuation, highlighting the favorable tolerability of colesevelam relative to older agents like cholestyramine, which often suffer from poor palatability and gastrointestinal discomfort.^22 Prior studies comparing tolerability have similarly favored colesevelam, with higher patient adherence and fewer withdrawals due to side effects.^23 Our findings corroborate these patterns and support wider adoption of colesevelam in BAD treatment protocols.

Emerging research into the interaction between bile acid sequestrants and gut microbiota suggests that agents like colesevelam may exert modulatory effects beyond bile binding. Animal and ex vivo models report altered Bacteroides-to-Firmicutes ratios and reductions in colonic secondary bile acids following sequestrant therapy, potentially impacting colonic inflammation and barrier integrity.^24 Although our study did not include microbiome profiling, the rapid clinical response observed suggests that direct bile acid removal remains the principal mechanism, rather than long-term microbial shifts. Nevertheless, future integration of metagenomic analysis would provide valuable insights into secondary therapeutic pathways.^25

Another strength of the study is its biomarker-integrated recruitment, utilizing SeHCAT retention testing to objectively confirm diagnosis. As SeHCAT is not widely available, a growing body of literature advocates for validated surrogate markers like serum C4 and FGF19 to guide empirical treatment and study enrollment.^26,27 While not feasible in all healthcare systems, incorporation of such diagnostic precision improves trial validity and enhances treatment effect detection. This methodology contrasts with symptom-based inclusion used in many earlier studies, which likely

introduced diagnostic misclassification and underestimation of treatment efficacy.^28 Our approach aligns with the trajectory toward precision-based gastroenterology.

In summary, this trial establishes high-grade evidence supporting colesevelam as an effective and well-tolerated therapy for confirmed bile acid diarrhea. The results not only confirm but extend prior data through rigorous design, statistically robust outcomes, and incorporation of validated diagnostic criteria. These findings have direct clinical relevance and may inform future guideline updates in the management of chronic diarrhea with suspected or proven bile acid malabsorption. Future studies should focus on comparative effectiveness, long-term remission durability, and molecular profiling to further optimize treatment strategies.^29,30

Conclusion

Colesevelam demonstrated significant efficacy and tolerability in patients with SeHCAT-confirmed bile acid diarrhea, resulting in improved stool parameters and quality of life. This study addresses prior gaps in evidence through biomarker-guided diagnosis and rigorous trial design. Future research should explore long-term outcomes, mechanistic pathways, and alternative diagnostic tools in broader populations.

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