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ABOUT COVER

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AIMS AND SCOPE

The primary aim of the *World Journal of Gastrointestinal Pharmacology and Therapeutics* (*WJGPT*, *World J Gastrointest Pharmacol Ther*) is to provide scholars and readers from various fields of gastrointestinal pharmacology and therapeutics with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGPT mainly publishes articles reporting research results obtained in the field of gastrointestinal pharmacology and therapeutics and covering a wide range of topics including acid-related disorders, functional gastrointestinal disorders, fundamentals of gastrointestinal pharmacology, *etc.*

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LETTER TO THE EDITOR

"Timing of percutaneous endoscopic gastrostomy tube placement in post-stroke patients does not impact mortality, complications, or outcomes": Commentary

Jonathan Willman, Brandon Lucke-Wold

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Abstract

In this commentary, we summarize some of the key points of the original paper "Timing of percutaneous endoscopic gastrostomy tube placement in post-stroke patients does not impact mortality, complications, or outcomes" and offer support for the proposed results. Specifically, we address how early percutaneous endoscopic gastrostomy (PEG) tube placement may reduce hospital length of stay and costs. We also discuss topics related to the article including PEG weaning and post-stroke nutritional formulation. However, we note that concerns purported by previous studies that early PEG placement may worsen outcomes are not fully addressed, and further research is needed.

Key Words: Percutaneous endoscopic gastrostomy tube; Post-stroke; Nutritional management; Rehabilitation; Dysphagia

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Core Tip: Here we summarize some of the key points of the original paper and offer support for the proposed results. Specifically, we address how early percutaneous endoscopic gastrostomy (PEG) tube placement may reduce hospital length of stay and costs. We also discuss topics related to the article including PEG weaning and post-stroke nutritional formulation. However, we note that concerns purported by previous studies that early PEG placement may worsen outcomes are not fully addressed, and further research is needed.

Citation: Willman J, Lucke-Wold B. "Timing of percutaneous endoscopic gastrostomy tube placement in post-stroke patients does not impact mortality, complications, or outcomes": Commentary. *World J Gastrointest Pharmacol Ther* 2023; 14(1): 1-3
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INTRODUCTION

Early percutaneous endoscopic gastrostomy (PEG) tube placement may reduce hospital length of stay and costs. Extensive PEG tube use in post-stroke patients highlights new topics of interest such as proper PEG weaning protocols and post-stroke nutritional formulation. In addition, further research is needed to fully address concerns raised by previous studies that early PEG placement may worsen certain patient outcomes.

ARTICLE FINDINGS AND RECENT SUPPORT

The findings of the study, "Timing of percutaneous endoscopic gastrostomy tube placement in post-stroke patients does not impact mortality, complications, or outcomes", indicate that early PEG tube placement may be associated with a shorter length of hospital stay and likely a reduction in costs[1]. This has been further supported by recent research[2]. In addition, this concept that early PEG placement may reduce hospital stay has been supported by research in a number of diverse fields, including post-head and neck surgery recovery[3]. Furthermore, the authors' suggestion that delayed PEG placement may be associated with higher rates of complications is endorsed by recent studies that have found higher pneumonia rates in post-stroke patients treated with a nasogastric tube instead of PEG[4,5].

ARTICLE LIMITATIONS

This study by Reddy *et al*[1] highlights a number of factors that support early PEG placement in post-stroke patients, including that there may be no significant difference in mortality outcomes between early and late PEG placement, and that early PEG placement may reduce hospital length of stay and feasibly cost of stay. However, the authors do not fully address the concerns purported by the FOOD trial that while early PEG placement may be associated with reduced mortality rates, it was also associated with higher rates of patients living with worse outcomes[6]. While it is possible that the higher rates of patients with poorer outcomes is due only to higher rates of survival in those with greater complications who would have otherwise died, further research is needed to elucidate this finding.

THE DIRECTION OF FUTURE RESEARCH AND THERAPEUTIC GUIDANCE

It has been well demonstrated that post-stroke patients are at a higher risk for malnutrition[7]. Recent research has shown that a nutritional regimen that is high in protein may rescue post-stroke muscle loss and promote recovery from dysphasia[8].

It is also worth noting that PEG tube weaning benefits from a multidisciplinary approach with swallowing assessment, swallowing therapy, and a steady increase in oral consumption until the PEG tube can be safely removed[9,10].

CONCLUSION

The findings of this study by Reddy *et al*[1] add substantially to the question of whether early PEG placement is beneficial both economically and therapeutically, but further research is needed for therapeutic guidance.

FOOTNOTES

Author contributions: Willman J contributed to conception, drafting the article, critical revision of the article; Lucke-Wold B contributed to conception, critical revision of the article.

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Basic Study

4 Cinnamic acid regulates the intestinal microbiome and short-chain fatty acids to treat slow transit constipation

Jiang JG, Luo Q, Li SS, Tan TY, Xiong K, Yang T, Xiao TB

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ORIGINAL ARTICLE

Basic Study

Cinnamic acid regulates the intestinal microbiome and short-chain fatty acids to treat slow transit constipation

Jin-Guang Jiang, Qian Luo, Shuang-Shuang Li, Tian-Ying Tan, Kai Xiong, Tao Yang, Tian-Bao Xiao

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Abstract

BACKGROUND

Slow transit constipation (STC) is a disorder with delayed colonic transit. Cinnamic acid (CA) is an organic acid in natural plants, such as *Radix Scrophulariae* (Xuan Shen), with low toxicity and biological activities to modulate the intestinal microbiome.

AIM

To explore the potential effects of CA on the intestinal microbiome and the primary endogenous metabolites-short-chain fatty acids (SCFAs) and evaluate the therapeutic effects of CA in STC.

METHODS

Loperamide was applied to induce STC in mice. The treatment effects of CA on STC mice were assessed from the 24 h defecations, fecal moisture and intestinal transit rate. The enteric neurotransmitters: 5-hydroxytryptamine (5-HT) and vasoactive intestinal peptide (VIP) were determined by the enzyme-linked immunosorbent assay. Hematoxylin-eosin and Alcian blue and Periodic acid Schiff staining were used to evaluate intestinal mucosa's histopathological performance and secretory function. 16S rDNA was employed to analyze the composition and abundance of the intestinal microbiome. The SCFAs in stool samples were quantitatively detected by gas chromatography-mass spectrometry.

RESULTS
CA ameliorated the symptoms of STC and treated STC effectively. CA ameliorated the infiltration of neutrophils and lymphocytes, increased the number of goblet cells and acidic mucus secretion of the mucosa. In addition, CA significantly increased the concentration of 5-HT and reduced VIP. CA significantly improved the diversity and abundance of the beneficial microbiome. Furthermore, the production of SCFAs [including acetic acid (AA), butyric acid (BA), propionic acid (PA) and valeric acid (VA)] was significantly promoted by CA. The changed abundance of *Firmicutes, Akkermansia, Lachnoclostridium, Monoglobus, UCG.005, Paenalcaligenes, Psychrobacter* and *Acinetobacter* were involved in the production of AA, BA, PA and VA.

CONCLUSION
CA could treat STC effectively by ameliorating the composition and abundance of the intestinal microbiome to regulate the production of SCFAs.

Key Words: Slow transit constipation; Cinnamic acid; Intestinal microbiome; Short-chain fatty acids; Intestinal motility

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Core Tip: Studies on the gut microbiome and its metabolites are increasingly in slow transit constipation (STC). In this study, we found that Cinnamic acid (CA) improved and treated STC effectively by ameliorating intestinal mucosa's histopathological performance and secretory function in STC mice induced by loperamide, with alpha and beta diversity significantly decreased. Meanwhile, CA ameliorated the composition and abundance of the intestinal microbiome.

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INTRODUCTION

Slow transit constipation (STC) is one of the most boresome disorders in the digestive system and characterized by delayed colonic transit, caused by either myopathy or neuropathy[1]. The severity of slow transit may be severe enough to cease spontaneous bowel movements completely. The proportion of STC in chronic idiopathic constipation was estimated at 42%[2]. STC has curtailed the quality of life, burdened psychological distress, and significantly increased the social and economic burden[3,4].

It is very hard to manage and treat STC clinically because of the unknown pathophysiologic mechanisms. Abnormalities of the enteric nervous system and neurotransmitters [such as vasoactive intestinal peptide (VIP), substance P (SP), nitric oxide synthase (NOS)], imbalance of intestinal microbiome and decreased number of interstitial cells of Cajal have been described as the slow transit colon in the STC patients[5-7]. Alterations of the intestinal microbiome in patients with chronic constipation are characterized by a relative decrease in beneficial bacteria and a parallel increase of potentially pathogenic or opportunistic microbiome[8]. Previous studies have revealed the intimate association between STC and altered abundance of the interstitial microbiome. A cross-sectional pilot study using 16S rRNA gene pyrosequencing indicated that the abundances of *Bacteroidetes* were decreased and the abundances of genera *Blautia*, *Coprococcus* and *Ruminococcus* were increased significantly in constipated patients[6]. When analyzed at the phylum level, a previous study revealed that the *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* were increased significantly in patients with chronic constipation[9]. Using culture-based methods, it was also indicated that *Faecalibacterium*, *Roseburia* and *Coprococcus* were increased significantly in constipated patients[10]. All these alterations of the intestinal microbiome influenced intestinal motility and metabolic function by changing the number of metabolites and the metabolic environment of the gut[11]. Short-chain fatty acids (SCFAs), the primary endogenous metabolites, were produced from the fermentation of undigested carbohydrates by intestinal bacteria. SCFAs could enhance the absorption of fluid and sodium absorption potentially aggravate STC symptoms[12]. A case-control study indicated that butyrate, acetate, and propionate levels were significantly lower in constipated patients[13]. Furthermore, a previous study demonstrated that the administration of SCFAs with 100-200 *mM* directly into rats

stimulated colonic motility and accelerated colonic transit[14]. In these regards, the regulation of regulating crobiome and the metabolism of SCFAs *via* interventional drugs may be essential to treat STC.

Cinnamic acid (CA) is an organic acid in natural plants, such as *Radix Scrophulariae* (Xuan Shen), that has low toxicity and with a broad spectrum of biological activities. A previous study showed that CA restrained gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*) bacteria effectively [15]. Furthermore, another study indicated that CA ameliorated lipopolysaccharide-induced inflammation and oxidative stress in mice[16]. However, a rare study clarified the therapeutic effects of CA in STC. In this study, we intend to explore the potential effects of CA on the intestinal microbiome and SCFAs and evaluate the therapeutic effects of CA in STC.

MATERIALS AND METHODS

Reagents

CA (CAS: 140-10-3) was purchased from Chroma Biotechnology Co. Ltd. (Chengdu, China) with HPLC purity ≥ 98%. Prucalopride (PRU) was purchased from Jiangsu Haosen pharmaceutical group Co., Ltd (Cat. No. H20183482). Loperamide was obtained from Xi'an Janssen Pharmaceutical Co., Ltd (Cat. No. LFJ8574). When applied to mice, all drugs were dissolved in sodium chloride injection (NS 0.9%).

Loperamide-induced STC mice and grouping

The model using loperamide-induced mice with STC was previously reported[17]. Briefly, specific pathogen-free (SPF), Balb/c mice (n = 50, 25 was male and 25 was female, weight: 20 ± 2 g, age: 4-6 wk) were purchased from Beijing Huahukang Animal Breeding Center (permission No. SCXK-(jing) 2019–0008). All mice were maintained under SPF conditions in a shelter sustained facility and provided with sterile food and water. All mice were randomly divided into the control group, model group, PRU group, CA with low-dose and high-dose groups (n = 10 per group) respectively. The mice in the model group were given loperamide at a dose of 9.6 mg/kg, once per day *via* oral gavage for 4 consecutive weeks. Mice in the positive group received 0.26 mg/kg·d^{-1} PRU (the equivalent doses of the clinic). Mice in the low-dose and high-dose CA group received 40 mg/kg·d^{-1} and 80 mg/kg·d^{-1} CA respectively, according to the study of Yan *et al*[18] and Wang *et al*[19]. PRU and CA were orally administered once daily for four weeks. The serum samples, stool samples in the intestine and colon tissues were collected when all mice were sacrificed on the 29th day. All collected samples were kept at -80 °C condition and then taken for further experiments.

Assessment of 24 h defecations, fecal moisture and intestinal transit rate

At the end of experiment, all mice were housed individually in metallic cages to collect feces once an hour for 24 h, and the feces number and weight were recorded. The fecal water content was calculated after drying the feces in a desiccator at 60 °C for 12 h, according to the equation: (wet weight-dry weight)/wet weight ×100%. To evaluate the intestinal transit rate, all mice in each group were gavaged with 0.2 mL Indian ink after 2 h at the end of the last treatment. After 24 h, mice were sacrificed. The intestinal transit rate was calculated according to the equation: traveled distance of Indian ink in the intestine (cm)/full length of intestine (cm) × 100%.

Measurement of 5-HT and VIP concentration

Two main enteric neurotransmitters: 5-hydroxytryptamine (5-HT) and VIP were determined by the enzyme-linked immunosorbent assay (ELISA). The serum concentration of 5-HT and the VIP content in the colon tissue was detected by the ELISA kits. ELISA kits of 5-HT (Cat No.: JYM0433Mo) and VIP (Cat No.: JYM0436Mo) were purchased from Colorful-Gene Biotechnology Co., Ltd. (www.jymbio.com, Wuhan, China). All assays were performed rigorously according to the manufacturer's instructions. The Synergy H1 Hybrid Reader (Biotech, United States) was applied to measure the relative optical density of 5-HT and VIP spectrophotometrically at a wavelength of 450 *nm*.

Hematoxylin-eosin and Alcian blue/periodic acid-Schiff staining of colon tissue

Mice were sacrificed at the end of the experiment. Parts of the colons were fixed in 4% paraformaldehyde cleared in xylene, embedded in paraffin, and cut into 5 mm thick slices. The histopathological performance of colon tissue was stained with hematoxylin-eosin (HE). Furthermore, the mucous cells in the colon were stained with Alcian blue/periodic acid-Schiff (AB/PAS). All experiment processes were performed according to the manufacturer's instructions.

Intestinal microbiome analysis by 16S rDNA

The total DNA in stool samples was extracted with a stool DNA kit (Omega Bio-Tek, Norcross, GA, United States). Then, the V3-4 hypervariable region of the bacterial 16S rRNA gene was amplified with the universal primers, forward (5'-3'): ACTCCTACGGGAGGCAGCAG and reverse (5'-3'): GGACTA-

CHVGGGTWTCTAAT (806R). The PCR products were purified using a QIAquick Gel Extraction Kit (QIAGEN, Germany), quantified using RT-PCR, and sequenced. The deep sequencing was performed on Miseq platform. After the run, image analysis, base calling and error estimation were performed using Illumina Analysis Pipeline Version 2.6. The raw data were screened and sequences were removed if they were shorter than 200 bp, had a low-quality score (≤ 20), contained ambiguous bases or did not match primer sequences and barcode tags. Finally, the dataset analysis was performed using the online platform of Majorbio Cloud Platform (www.majorbio.com).

Quantitative detection of SCFAs by gas chromatography-mass spectrometry

The SCFAs in stool samples were quantitatively detected by gas chromatography-mass spectrometry (GC-MS). All of the seven SCFAs, including acetic acid (AA), butyric acid (BA), caproic acid (CA-1), isobutyric acid (IBA), isovaleric acid (IVA), propionic acid (PA) and valeric acid (VA), were extracted as previously described[18]. Briefly, 50 mg of stool sample was used for metabolite extraction with 400 μL methanol-acetonitrile and 30 μL L-2-chlorophenyl alanine. After homogenization and ultrasonic extraction, the samples were incubated at -20 °C for 30 min and centrifuged for 10 min at 12000 rpm at 4 °C. Finally, 20 μL of supernatant from each sample was transferred to a vial for GC-MS analysis. The condition of GC-MS referred to the previous study[19]. All samples were evaluated in duplicate.

Statistics analysis

All data were presented as mean ± standard deviation and analyzed with the SPSS software program (version 21.0). Data were presented using one-way ANOVA followed by an LSD test. $P < 0.05$ was considered statistically significant and $P < 0.01$ was highly significant. R software (version 4.0.4) and GraphPad Prism software for Windows (version 8.02; Inc., San Diego, United States) were utilized for the visible presentation of all results.

RESULTS

CA increased 24 h defecations, fecal moisture and intestinal transit rate of STC mice

The pharmacological effects of CA on STC were evaluated from the 24 h defecations, fecal moisture and intestinal transit rate aspects. As presented in Figure 1A and B, mice in the STC model group showed more feces remaining in the colon and shorter length than the control group. Meanwhile, the 24 h defecations in the STC model group was significantly decreased (Figure 1C). After treated by CA with 40 mg/kg·d^{-1} and 80 mg/kg·d^{-1}, the number of fecal remnants in the colon (Figure 1B) was significantly decreased and 24 h defecations (Figure 1C) was significantly increased when compared with the STC model group. In addition, the fecal water content also was significantly increased by the CA treatment, especially in the CA with high doses group (Figure 1D). Parallelly, the intestinal transit rate was significantly higher in the CA with high doses group compared with the STC model group (Figure 1E). Those results indicated that CA could ameliorate the symptoms of STC and treat STC effectively.

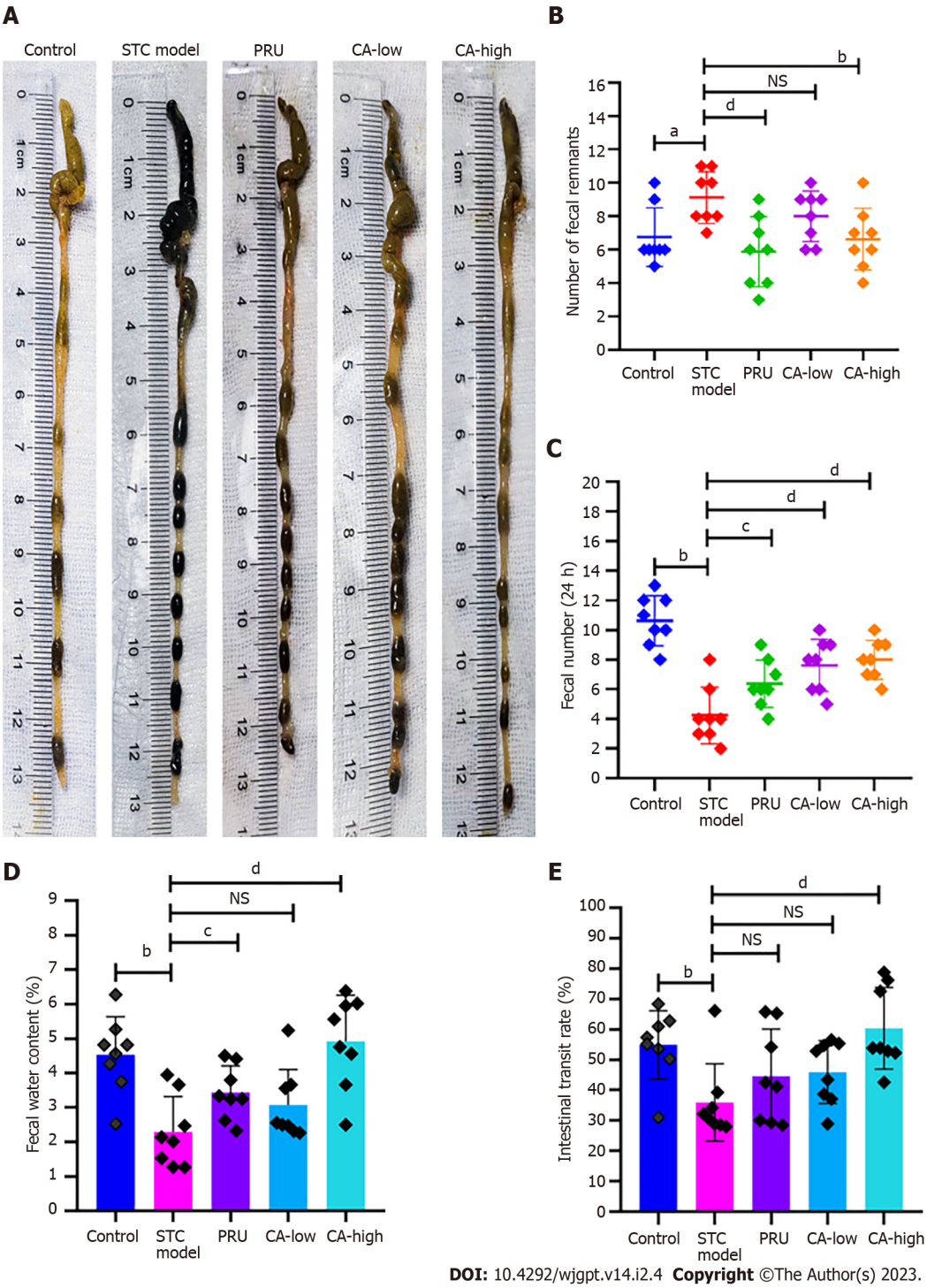
CA ameliorated the histopathological performance and secretory function of intestinal mucosa in STC mice

As presented in Figure 2A, mice in the control group showed the mucosa, muscular and goblet cells were normal. However, the model group showed that the thickness of the mucosa and muscular was significantly thinner. The mucosal integrity was compromised and chronic inflammation was observed in the mucosa, presented with a large number of eosinophilic infiltration, mainly in the lamina propria. Furthermore, the number of goblet cells was significantly reduced. Compared with the model group, the thickness of the mucosa and muscular were increased significantly, inflammatory cell infiltration was reduced, mucosa was smoother, and the structure of glandular was gradually restored and arranged more neatly in the PRU group. The CA group with low and high doses showed smoother mucosa, more intact morphology and structure of glandular (secreting mucus, lubricating the intestinal tract, and facilitating bowel movements), less infiltration of neutrophils and lymphocytes, and higher numbers of phagocytes compared to the PRU group (Figure 2A).

Then, the secretory function of goblet cells in the mucosa was tested. As presented in Figure 2B, the secretion of acidic mucus (the blue part) was significantly decreased in the model group compared with the control group. The acidic mucus secreted by the goblet cells in the PRU group increased slightly. Conversely, the secretion of acidic mucus was significantly increased in the CA group, especially in the CA with high doses group.

CA increased the concentration of 5-HT and reduced VIP

As presented in Table 1 and Figure 3A, the serum concentration of 5-HT was significantly decreased in the STC model group, which was significantly lower than the control group ($P < 0.01$). In the PRU group, 5-HT concentration was significantly increased, even higher than the control group. In the CA group with low and high doses, 5-HT concentration was significantly increased compared with the STC



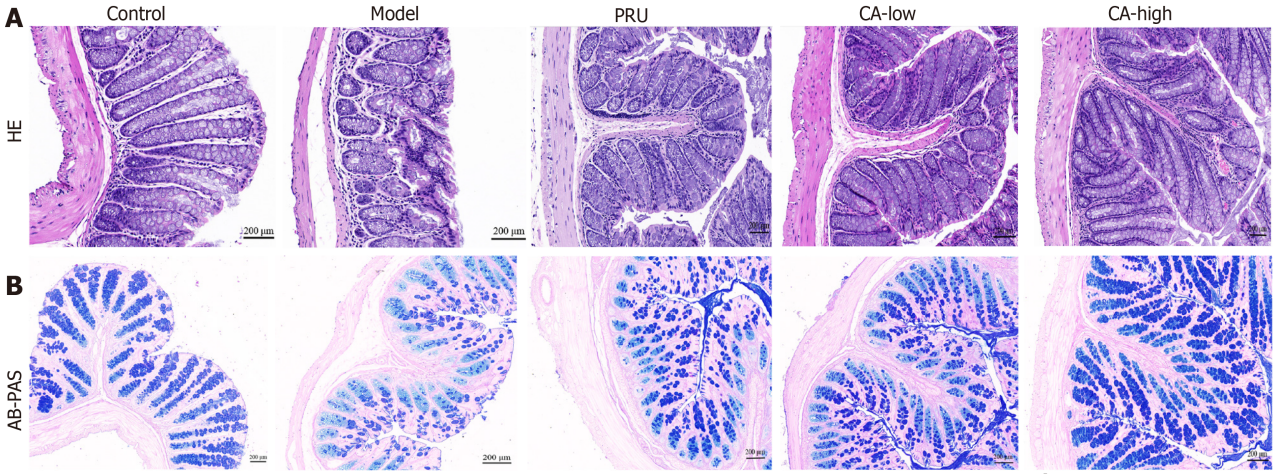
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Figure 1 Pharmacological effects of cinnamic acid on slow transit constipation mice. A: Number of fecal remnants in the colon of mice in each group (n = 8); B: Number of fecal remnants in the colon of mice in each group (n = 8); C: 24 h defecations of mice in each group (n = 8); D: Fecal water content of mice in each group (n = 8); E: Intestinal transit rate of mice in each group (n = 8). $^{a}P < 0.05$ and $^{b}P < 0.01$ versus the control group; $^{c}P < 0.05$ and $^{d}P < 0.01$ versus the slow transit constipation model group. NS: Not significant. PRU: Prucalopride; CA-low: Cinnamic acid with low dose; CA-high: Cinnamic acid with high dose.

model group ($P < 0.01$, Table 1 and Figure 3A). On the contrary, the VIP concentration in the colon tissue was increased significantly in the STC model group (Table 1 and Figure 1B). After treated by CA with low and high doses, the content of VIP was significantly decreased compared with the STC model group ($P < 0.01$, Table 1 and Figure 3B).

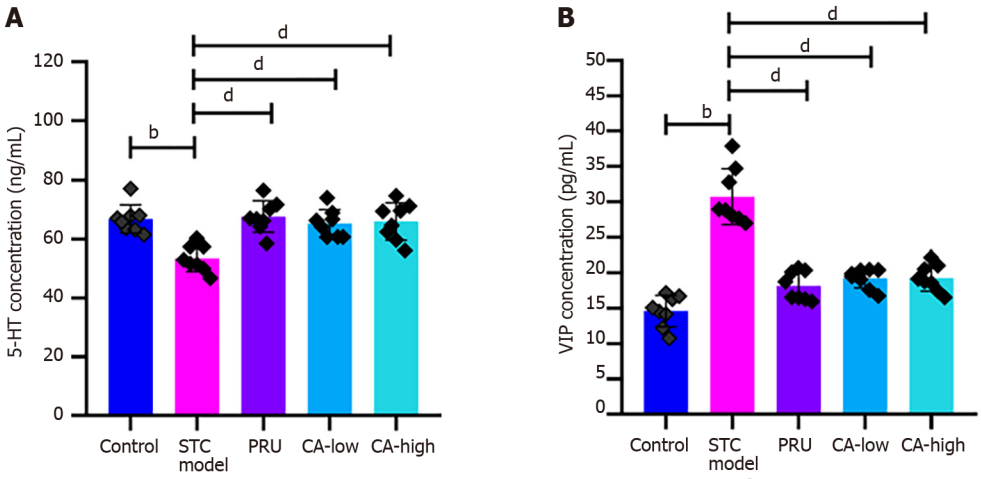
CA improved the alpha diversity of intestinal microbiome in STC mice

The Shannon index, one of the diversity indices for estimating microbial diversity, was applied to evaluate the alpha diversity of the intestinal microbiome in different groups.



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Figure 2 Hematoxylin-eosin and Alcian blue/periodic acid-Schiff staining of each group of mice. A: HE staining of each group of mice; B: Alcian blue/periodic acid-Schiff staining of each group of mice. PRU: Prucalopride; CA-low: Cinnamic acid with low dose; CA-high: Cinnamic acid with high dose.



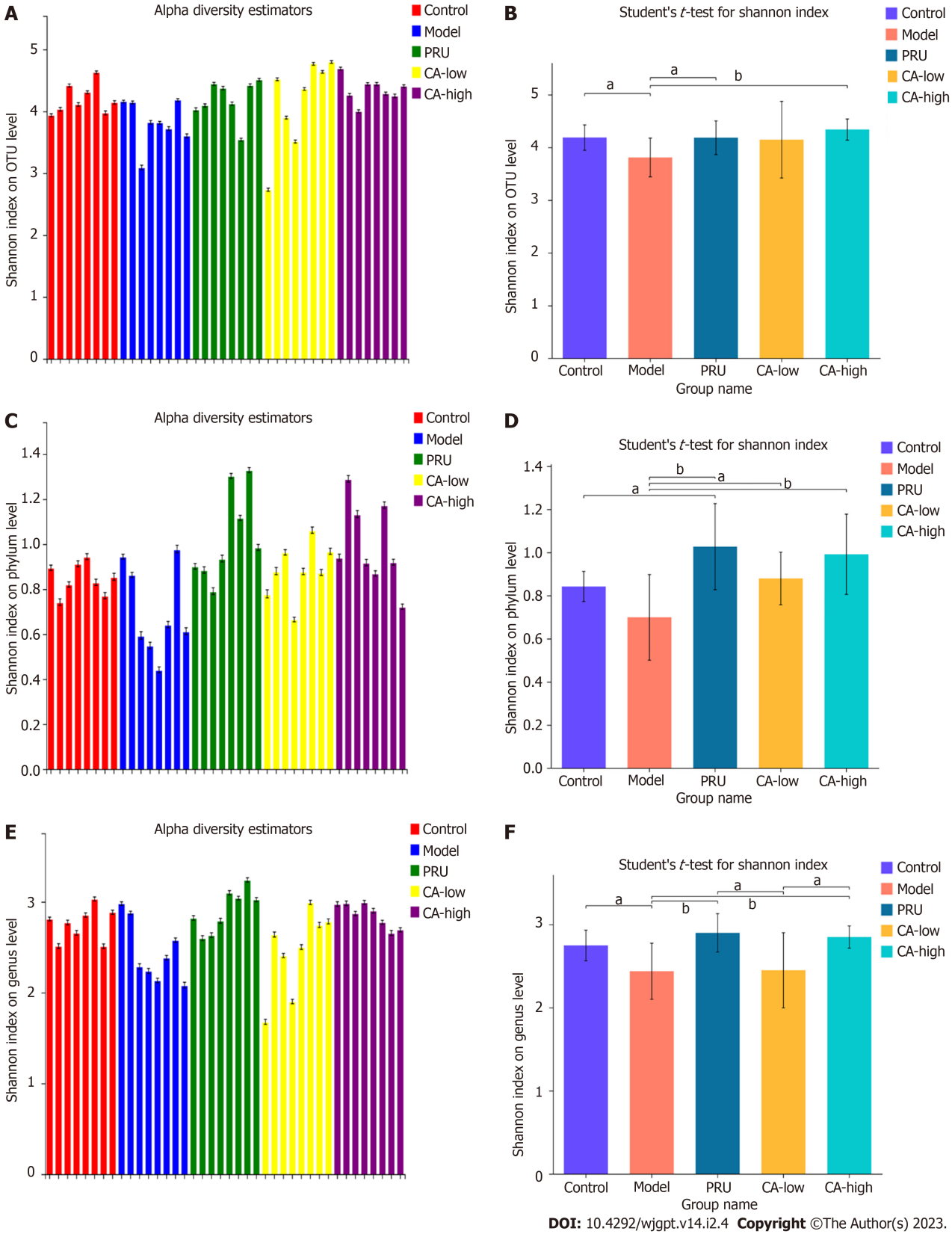
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Figure 3 Effects of Cinnamic acid on the concentration of 5-HT and vasoactive intestinal peptide. A: Serum concentration of 5-hydroxytryptamine in each group of mice (n = 8); B: Content of vasoactive intestinal peptide in the colon of mice in each group (n = 8). $^{b}P < 0.01$ versus the control group; $^{d}P < 0.01$ versus the slow transit constipation model group. PRU: Prucalopride; CA-low: Cinnamic acid with low dose; CA-high: Cinnamic acid with high dose.

The higher the Shannon index, the greater the community's diversity in the intestinal microbiome. As presented in Figure 4A and B, the Shannon index was significantly decreased at the operational taxonomic units (OTU) level compared with the control group ($P < 0.05$) and the CA with doses group ($P < 0.01$). In addition, the Shannon index also decreased significantly in the model group at the phylum (Figure 4C and D) and genus level (Figure 4E and F). After CA treatment, the Shannon index was upgraded significantly. Altogether, these results indicated that CA could improve the alpha diversity of the intestinal microbiome in STC mice.

CA increased the beta diversity of intestinal microbiome in STC mice

Principal coordinates analysis (PCoA) of Bray-Curtis distance matrices was carried out for beta diversity determination among different groups. As shown in Figure 5A, evident separation of the microbiome was observed on the two-dimensional PCoA plots among different groups. The microbiome separated significantly from the control and CA in the model group with the high doses group. The Venn plots (Figure 5B) indicated the co-species number in all groups was 506. In the model group, the species number was lower than in the remaining four groups (the control, PRU, CA-low and CA-high groups). A hierarchical clustering analysis at the OUT (Figure 5C), phylum (Figure 5D) and genus level (Figure 5E) showed significant differences between each group. The CA-treated samples were clustered separately from the model group but close to the control group, indicating that CA could alleviate the distribution of species in microbial beta diversity.

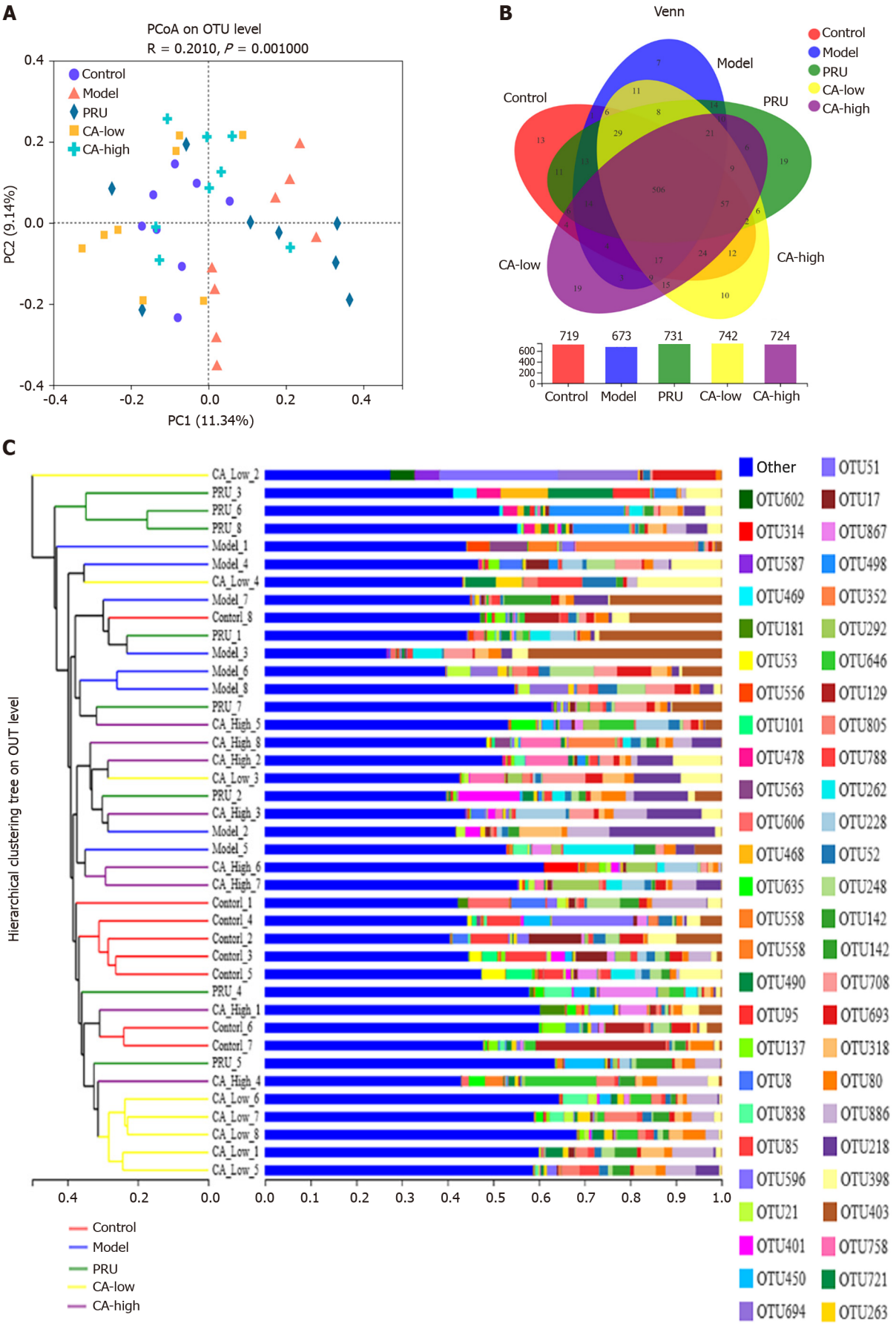


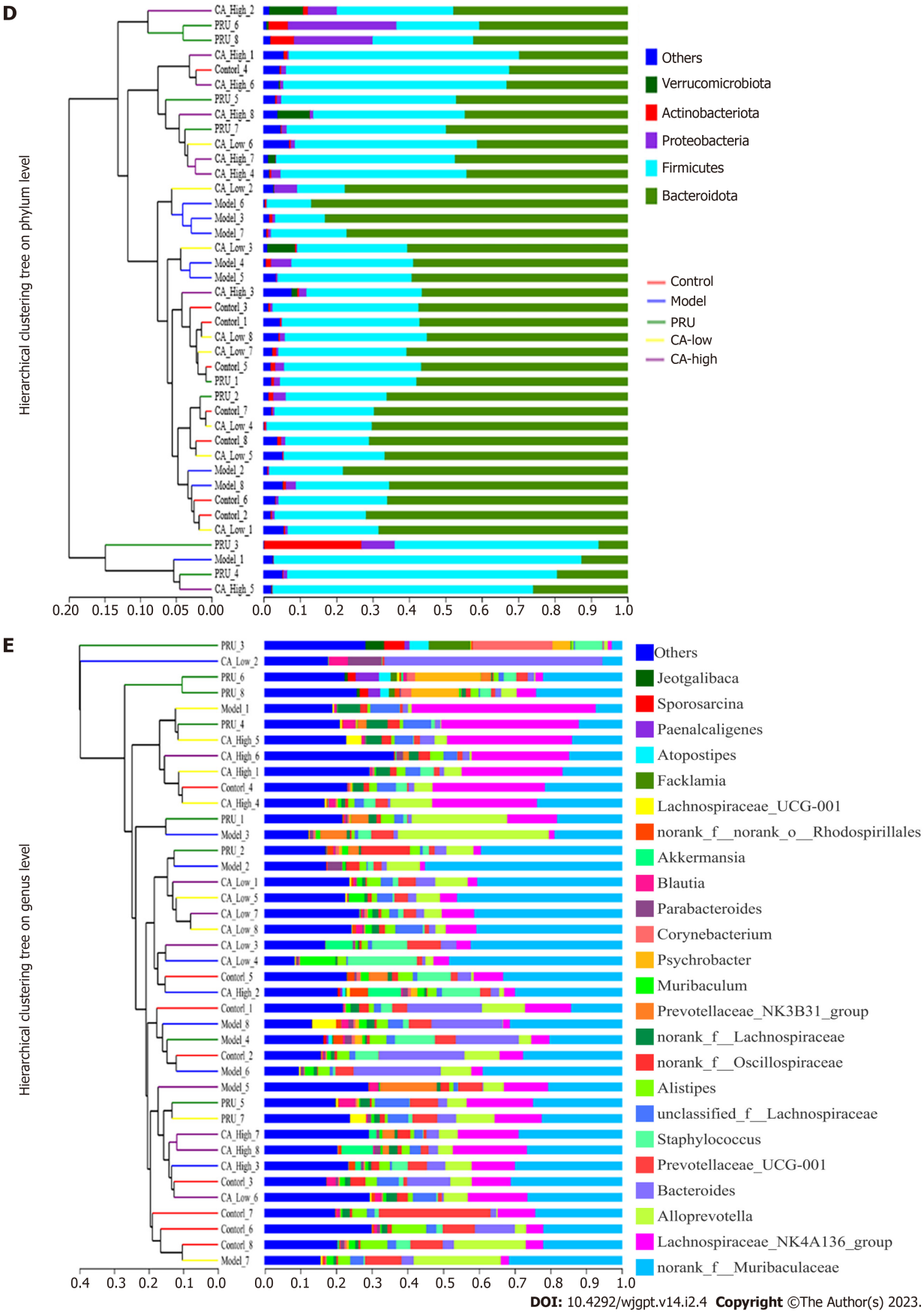
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Figure 4 Alpha diversity of intestinal microbiome in each group of mice (*n* = 8). A: Shannon index evaluation of each group of mice at the OTU level; B: Difference test of Shannon index at the OTU level; C: Shannon index evaluation of each group of mice at the phylum level; D: Difference test of Shannon index at the phylum level; E: Shannon index evaluation of each group mice at the genus level; F: Difference test of Shannon index at the genus level; $^{a}P < 0.05$ and $^{b}P < 0.01$. PRU: Prucalopride; CA-low: CA with low dose; CA-high: CA with high dose.

CA promoted the composition and abundance of the intestinal microbiome in STC mice

The species difference analysis was conducted to identify the specific microbiome in different groups. The linear discriminant analysis effect size (LefSe) (Figure 6A) based on the linear discriminant analysis

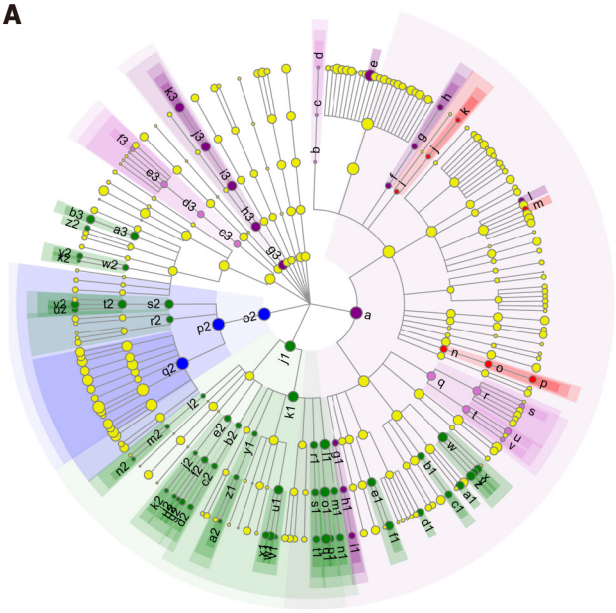

A
PCoA on OTU level
R = 0.2010, P = 0.001000
Control
Model
PRU
CA-low
CA-high
PC2 (9.14%)
PC1 (11.34%)
B
Venn
Control
Model
PRU
CA-low
CA-high
719
673
731
742
724
C
Hierarchical clustering tree on OUT level
Other
OTU602
OTU314
OTU587
OTU469
OTU181
OTU53
OTU556
OTU101
OTU478
OTU563
OTU606
OTU468
OTU635
OTU558
OTU558
OTU490
OTU95
OTU137
OTU8
OTU838
OTU85
OTU596
OTU21
OTU401
OTU450
OTU694
OTU51
OTU17
OTU867
OTU498
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OTU805
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OTU262
OTU228
OTU52
OTU248
OTU142
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OTU758
OTU721
OTU263



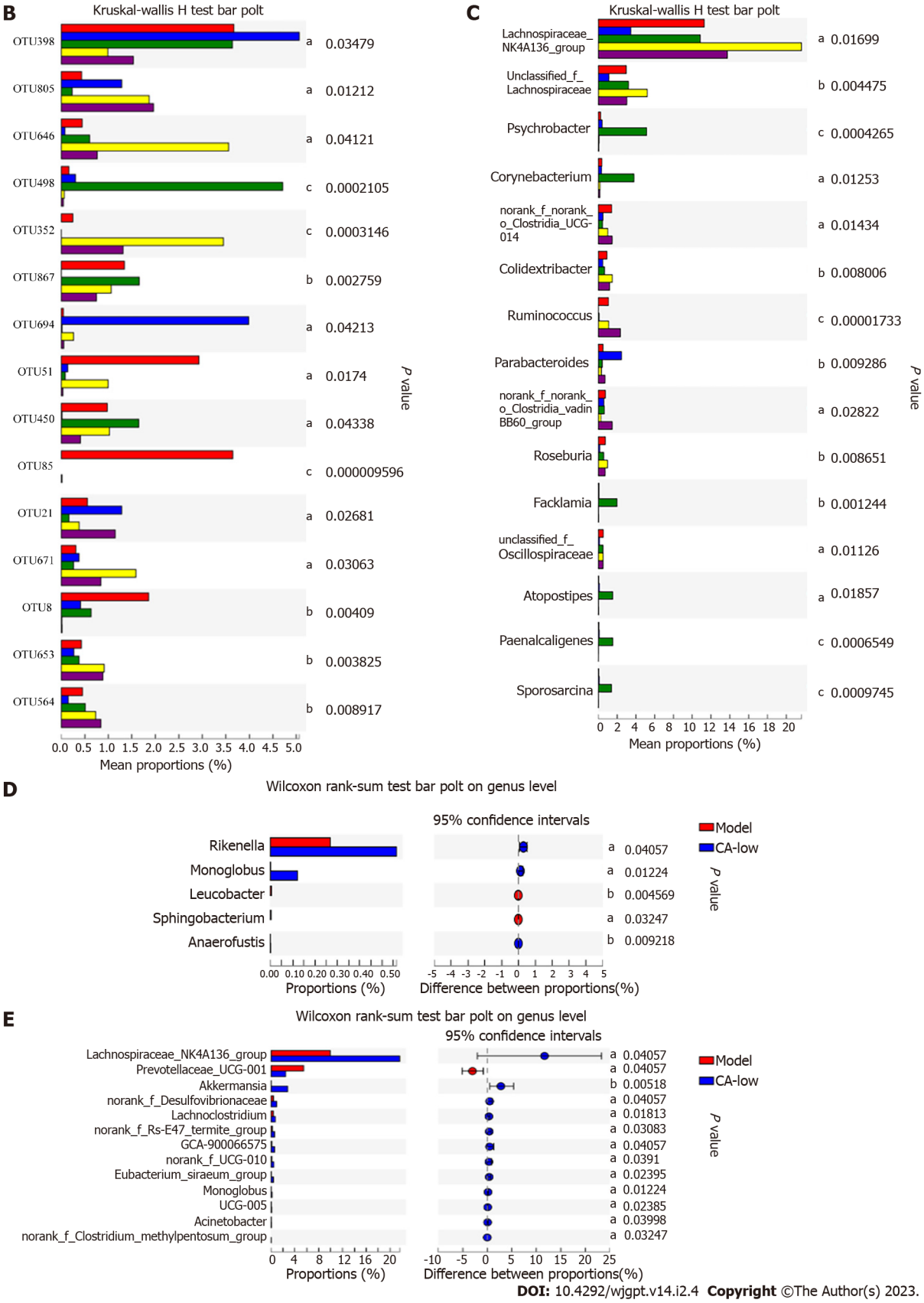
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Figure 5 Beta diversity of intestinal microbiome in each group of mice (*n* = 8). A: PcoA plot at the operational taxonomic units (OTU) level; B: Venn plot at the OTU level; C: Hierarchical clustering tree at the OTU level; D: Hierarchical clustering tree at the phylum level; E: Hierarchical clustering tree at the genus level; PRU: Prucalopride; CA-low: Cinnamic acid with low dose; CA-high: Cinnamic acid with high dose.

A



a : p__Firmicutes
b : o__Eubacteriales
c : f__Anaerofustaceae
d : g__Anaerofustis
e : g__Lachnospiraceae_NK4A136_group
f : o__unclassified_c__Clostridia
g : f__unclassified_c__Clostridia
h : g__unclassified_c__Clostridia
i : o__norank_c__Clostridia
j : f__norank_o__norank_c__Clostridia
k : g__norank_f__norank_o__norank_c__Clostridia
l : g__UCG-005
m : g__NK4A214_group
n : o__Monoglobales
o : f__Monoglobaceae
p : g__Monoglobus
q : o__Erysipelotrichales
r : f__Erysipelotrichaceae
s : g__unclassified_f__Erysipelotrichaceae
t : f__Erysipelatoclostridiaceae
u : g__Erysipelatoclostridium
v : g__Candidatus_Stoquefichus
w : f__Aerococcaceae
x : g__Aerosphaera
y : g__Aerococcus
z : g__Facklamia
a1 : g__Jeotgalibaca
b1 : f__Enterococcaceae
c1 : g__Enterococcus
d1 : g__Bacillus
e1 : f__Planococcaceae
f1 : g__Sporosarcina
g1 : o__Mycoplasmatales
h1 : f__Mycoplasmataceae
i1 : g__Mycoplasma
j1 : p__Proteobacteria
k1 : c__Gammaproteobacteria
l1 : o__Pseudomonadales
m1 : f__Pseudomonadaceae
n1 : g__Pseudomonas
o1 : f__Moraxellaceae
p1 : g__Acinetobacter
q1 : g__Psychrobacter
r1 : o__Aeromonadales
s1 : f Aeromonadaceae
t1 : g__Oceanisphaera
u1 : f__Alcaligenaceae
v1 : g__Alcaligenes
w1 : g__Paenalcaligenes
x1 : g__Oligella
y1 : o__Xanthomonadales
z1 : f__Xanthomonadaceae
a2 : g__Stenotrophomonas
b2 : o__Caulobacterales
c2 : f__Caulobacteraceae
d2 : g__Brevundimonas
e2 : o__Rhizobiales
f2 : f__Rhizobiaceae
g2 : g__Paenochrobactrum
h2 : g__unclassified_f__Rhizobiaceae
i2 : g__Pseudochrobactrum
j2 : f__Devosiaceae
k2 : g__Devosia
l2 : o__Rhodobacterales
m2 : f__Rhodobacteraceae
n2 : g__Paracoccus
o2 : p__Bacteroidota
p2 : c__Bacteroidia
q2 : o__Bacteroidales
r2 : o__Flavobacteriales
s2 : o__Sphingobacteriales
t2 : f__Sphingobacteriaceae
u2 : g__Sphingobacterium
v2 : g__unclassified_f__Sphingobacter
w2 : f__Microbacteriaceae
x2 : g__Microbacterium
y2 : g__Leucobacter
z2 : g__Glutamicibacter
a3 : f__Demequinaceae
b3 : g__norank_f__Demequinaceae
c3 : c__Coriobacteriia
d3 : o__Coriobacteriales
e3 : f__Eggerthellaceae
f3 : g__unclassified_f__Eggerthellacea
g3 : p__Verrucomicrobiota
h3 : c__Verrucomicrobiae
i3 : o__Verrucomicrobiales
j3 : f__Akkermansiaceae
k3 : g__Akkermansia



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Figure 6 The composition and abundance of the intestinal microbiome in each group of mice (*n* = 8). A: LefSe analysis of the significantly differential microbiome in each group; B: Differential comparison between multiple groups at the operational taxonomic units level; C: Differential comparison between multiple groups at the genus level; D: Differential comparison between model and CA-low group at the genus level; E: Differential comparison between model and CA-high group at the genus level. $^{a}P < 0.05$, $^{b}P < 0.01$ and $^{e}P < 0.001$. PRU: Prucalopride; CA-low: Cinnamic acid with low dose; CA-high: Cinnamic acid with high dose.

showed the abundance of *p__Bacteroidota.c__Bacteroidia.o__Bacteroidales* was significantly increased in the model group. The abundance of *p__Proteobacteria.c__Gammaproteobacteria.o__Pseudomonadales. f__Moraxellaceae.g__Acinetobacter was* significantly increased in the PRU group. After being treated by CA, the abundance of *p__Firmicutes.c__Clostridia.o__Eubacteriales* was increased significantly in the low doses of CA group. In addition, the abundance of *p__Firmicutes.c__Clostridia* and *p__Verrucomicrobiota. c__Verrucomicrobiae. o__Verrucomicrobiales* were increased significantly in the high doses of CA group (Figure 6A). In terms of bacterial composition at the OTU level, OTU 398 and OTU 694 were significantly increased in the model group than in the remaining four groups. After being treated by CA, OTU646, OTU 352, OTU 671 and OTU 653 were significantly increased (Figure 6B). Then, we identified the specific microbiome at the genus level. Overall, the significantly statistically significant species were *norank_f__Muribaculaceae*, *Colidextribacter*, *Ruminococcus*, *Lachnospiraceae_NK4A136_group*, *Alloprevotella*, *Bacteroides* and *Prevotellaceae_UCG-001* (Figure 6C). When compared the model group with the low doses of CA group, the *g_Rikenella, g_Monoglobus and g_Anaerofustis were* significantly increased (Figure 6D). When compared with the high doses of CA group, the *Lachnospiraceae_NK4A136_group, g_Akkermansia, norank_f__Desulfovibrionaceae, g_Lachnoclostridium, g_Monoglobus* and *g_Acinetobacter* were increased significantly (Figure 6E).

CA changed the phenotypes and functions of the intestinal microbiome in STC mice

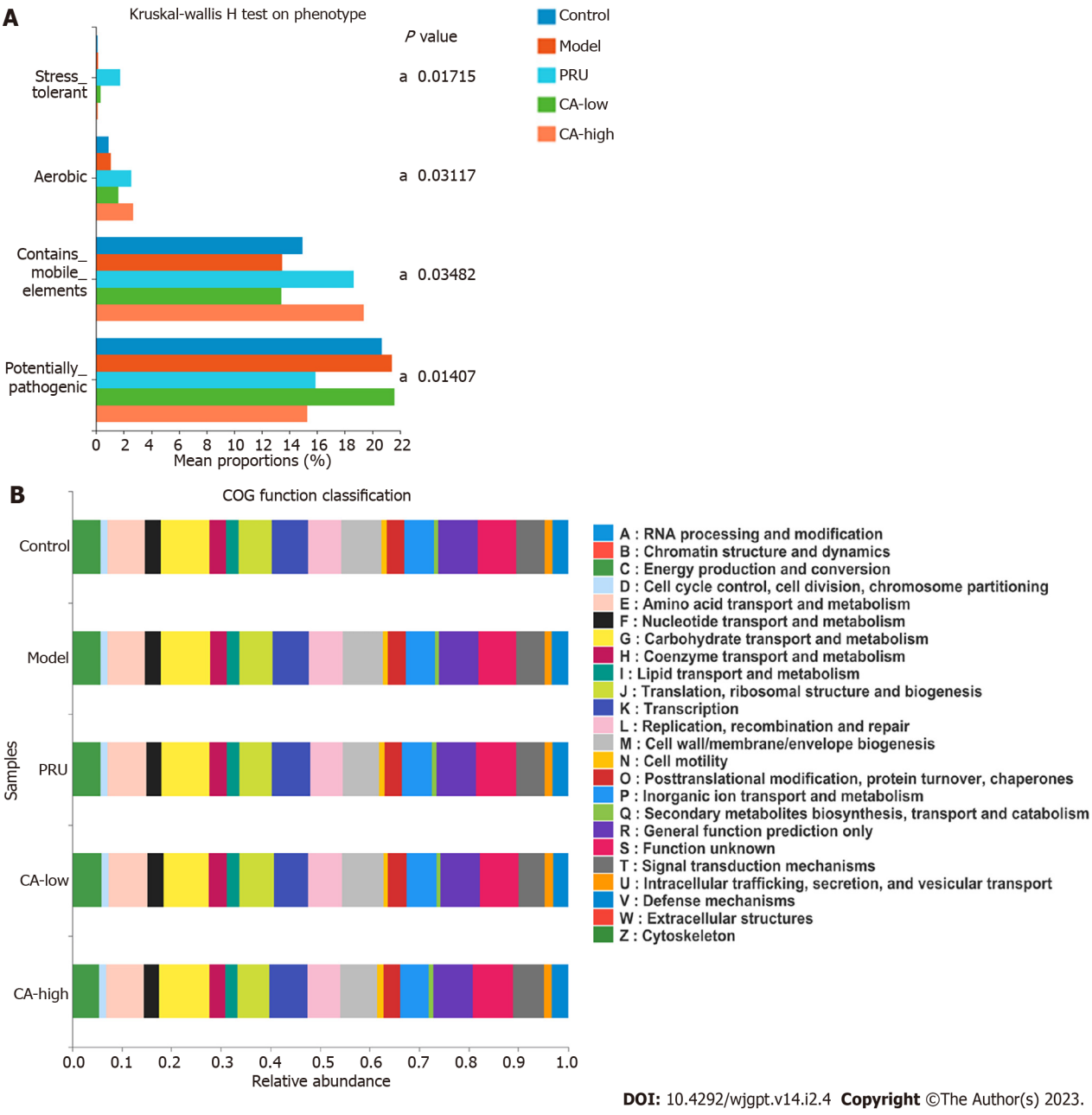
The BugBase was applied to predict the phenotypes based on the relative abundance of samples in different groups. Results indicated the phenotypes of stress-tolerant, aerobic, containing mobile elements and potentially pathogenic were predicted in different groups. The phenotypes of potentially pathogenic were increased significantly in the model group. Conversely, the phenotypes of aerobic and containing mobile elements were significantly increased in the high doses of CA group (Figure 7A). Then, the PICRUSt package of 16S amplification sequencing results was used to predict the biological functions. Results revealed that the functions of energy production and conversion, amino acid transport and metabolism, carbohydrate transport and metabolism, transcription were significantly improved by CA treatment (Figure 7B). Conclusively, CA mainly changed the phenotypes of aerobic and containing mobile elements and improved the biological functions of energy production and conversion, amino acid transport, and metabolism to regulate intestinal microbiome diversity.

CA upregulated the content of SCFAs via the intestinal microbiome in STC mice

A previous study indicated that the level of SCFAs in the stool could be involved in STC development [20-22]. Thus, the SCFAs in stool samples were quantitatively detected by GC-MS. The comparison between multiple groups showed that the content of SCFAs was decreased in the model group (Figure 8A). After being treated by CA, the content of AA and BA was increased (Figure 8A). The comparison between the model group and the low doses of CA group showed that the content of SCFAs was not increasing except for the BA (Figure 8B). However, the content of AA, BA and VA was increased in the high doses of CA group (Figure 8C). Then, the correlation between the dominant microbiome and SCFAs was analyzed by Spearman methods. Results indicated all content of SCFAs were negatively correlated with *g_Parabacteroides* and positively correlated with *g_Corynebacterium* (Figure 8D). The AA level was significantly decreased with the higher abundance of *g_Parabacteroides* ($P < 0.05$). The level of PA was significantly increased with the higher abundance of *g_Paenalcaligenes* ($P < 0.01$, Figure 8D) and *g_Psychrobacter* ($P < 0.05$, Figure 8D). In addition, the *g_Rikendlla* regulated by low doses of CA significantly increased the level of AA (Figure 8E). In the high doses of CA, most SCFAs levels were increased with the specific microbiome regulated by high doses of CA. The level of BA and VA was significantly increased with *g_UCG.005* ($P < 0.05$, Figure 8F), but the level of CA-1 was significantly decreased with *g__norank_f__Rs-E47_termite_group* ($P < 0.01$, Figure 8F). All mentioned results identified that CA could ameliorate the composition and abundance of the intestinal microbiome to regulate the content and production of SCFAs in STC mice.

DISCUSSION

There is increasing evidence indicating that the alterations of the intestinal microbiome and its metabolites are the pivotal pathophysiologic mechanism of STC. This study found that the alpha and beta diversity were significantly decreased in the STC mice induced by loperamide. In addition, the abundance of pathogenic or opportunistic bacteria, such as Bacteroides, and the phenotypes of potentially pathogenic were increased significantly in the STC mice. Meanwhile, the SCFAs, including AA, BA, IBA and VA, were decreased significantly in the STC mice compared with the normal control mice. Subsequently, we found that the organic acid: CA improved the symptoms of STC and treated STC effectively. Furthermore, CA ameliorated intestinal mucosa's histopathological performance and secretory function in STC mice. CA, especially with high dose (80 mg/kg·d^{-1}) also improved the alpha and beta diversity of the intestinal microbiome and significantly promoted *Firmicutes*' composition and abundance, *Verrucomicrobiota*, *Ruminococcus*, *Akkermansia*, *Lachnoclostridium Monoglobus* and *Acinetobacter* . Meanwhile, CA upregulated the level of AA, BA and VA *via* ameliorating the composition and

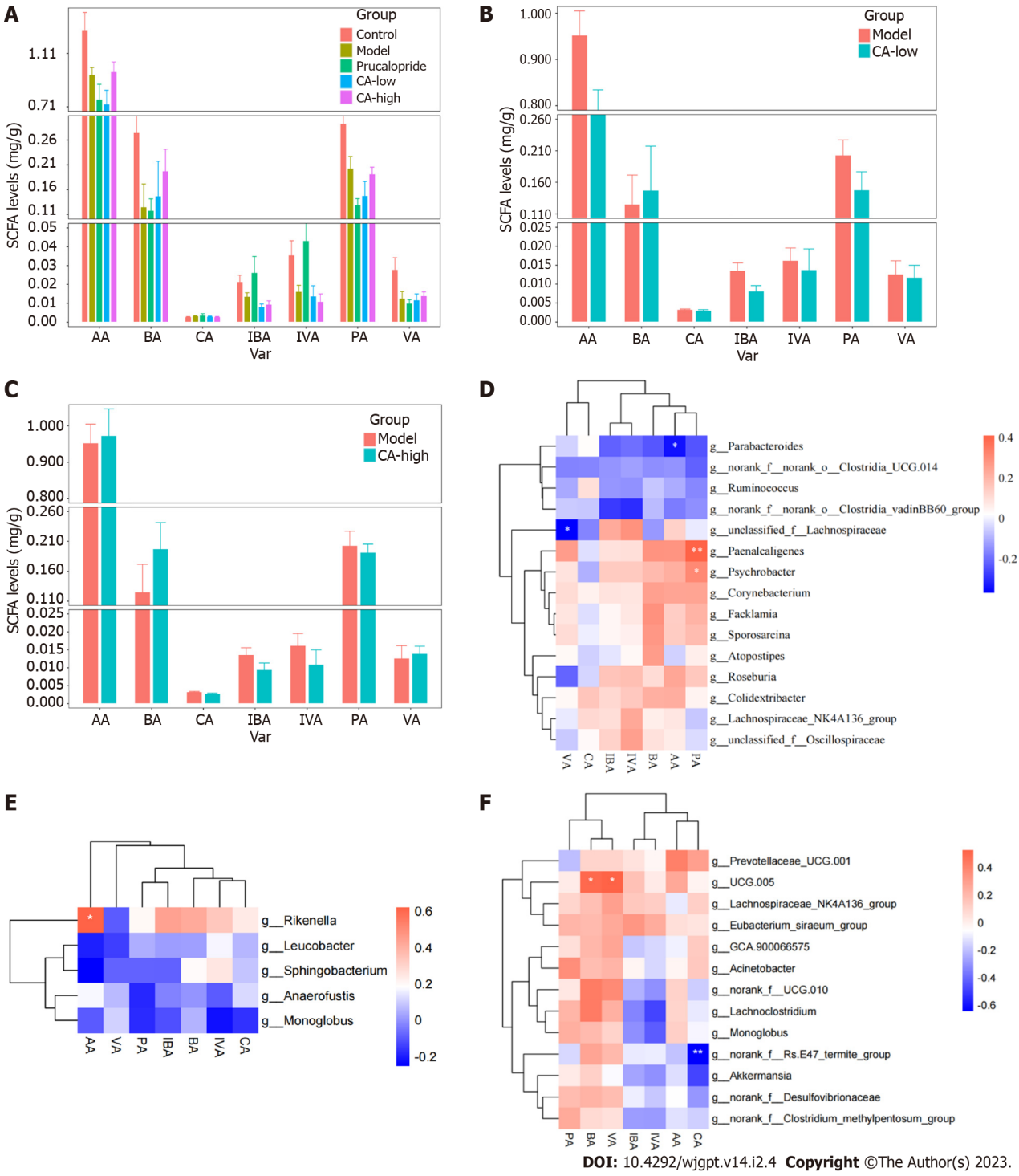


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Figure 7 Prediction of phenotypes and biological functions for the significantly differential microbiome in each group. A: Prediction of phenotypes for the significantly differential microbiome in each group; B: Prediction of biological functions for the significantly differential microbiome in each group. $^{a}P < 0.05$. PRU: Prucalopride; CA-low: Cinnamic acid with low dose; CA-high: Cinnamic acid with high dose.

abundance of the intestinal microbiome.

There has been increasing study regarding the direct association between the intestinal microbiome and gut motility and constipation. A recent study in germ-free mice (without gastrointestinal microbiota) showed that the colon transit time and gastric emptying were prolonged compared with the wild-type mice[23]. The colonization of *L.acidophilus*, *Bifidobacterium*, or *Clostridium tabificum* into germ-free rats accelerated the gut transit time and small-bowel migrating motor complexes. However, the colonization of *E. coli* significantly inhibited intestinal myoelectric activity[24]. In a murine study, the administration of loperamide significantly increased the abundance of *Bacteroides* and *Firmicutes*, and decreased the abundance of *Lachnospiraceae*. Consequently, the colonic contractility was significantly decreased and prolonged colon transit time[25]. In addition, in the loperamide-induced mice with STC, dysbiosis was also observed in intestinal bacteria. The abundance of *Bacteroidetes* was decreased and the *Firmicutes* and *Proteobacteria* increased significantly[26]. On the contrary, a decreasing abundance of *Clostridiales* and *Lactobacillales* and a significantly increasing in *Bacteroidales* abundance was noted in the loperamide-induced constipation rats[27]. Our study also found that the diversity and composition of the intestinal microbiome were dysbiotic, identifying the association between intestinal bacteria dysbiosis and the development of STC. Based on previous studies[28,29], we speculated that CA was



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Figure 8 Quantitative analysis of short-chain fatty acids and their correlation with the dominant microbiome (*n* = 8). A: Short-chain fatty acids (SCFAs) level in each group; B: SCFAs level in model and CA-low group; C: SCFAs level in model and CA-high group; D: Heatmap for the correlation between SCFAs and differential microbiome in each group; E: Heatmap for the correlation between SCFAs and differential microbiome in CA-low group; F: Heatmap for the correlation between SCFAs and differential microbiome in CA-high group. PRU: Prucalopride; CA-low: Cinnamic acid with low dose; CA-high: Cinnamic acid with high dose.

absorbed into the bloodstream mainly in the duodenum and jejunum and indirectly affected on the intestinal tract and the intestinal flora. However, no relevant experiments were designed to prove this in our study. Therefore, the study of absorption and metabolism of CA in STC mice will help to systematically elucidate the mechanism of action of CA in the treatment of STC.

SCFAs have been verified to affect the gut motility and contractility, colonic transit time, mucus production and the gut-brain axis. The alterations of the intestinal microbiome could regulate the production of SCFAs by changing the intestinal environment. Butyrate stimulates the Na and Cl absorption in the intestine and accelerates colon transit[12]. Butyrate also significantly increased the

Table 1 Concentration of 5-hydroxytryptamine and vasoactive intestinal peptide in each group of mice

Groups (n = 8)	5-HT (ng/mL)	VIP (ng/mL)
Control	66.83 ± 4.50	14.64 ± 2.08
STC Model	53.48 ± 4.23[b]	30.73 ± 3.70[b]
PRU	67.69 ± 5.00[d]	18.18 ± 1.92[d]
CA-low	65.31 ± 4.44[d]	19.28 ± 1.30[d]
CA-high	66.00 ± 5.93[d]	19.31 ± 1.75[d]

[b]P < 0.01 versus the control group.
[d]P < 0.01 versus the slow transit constipation model group.
5-HT: 5-hydroxytryptamine; CA: Cinnamic acid; PRU: Prucalopride; VIP: Vasoactive intestinal peptide; STC: Slow transit constipation.

colonic muscle contractions and promoted colonic transit by increasing the proportion of choline acetyltransferase in rats' enteric nervous system[30]. In addition, another study *in vitro* has shown that butyrate, propionate, and valerate induced the phasic contractions in the middle and distal colon *via* connecting the mucosal receptors to enteric and/or vagal nerves[31]. More and more studies have indicated that the intestinal microbiome regulates the level of SCFAs. A study predicted that the genus of *Coprococcus*, Roseburia, and *Faecalibacterium* increased the level of butyrate in constipation patients [6]. de Meij *et al*[32] found an increase in *Bacteroides fragilis*, *Bacteroides ovatus*, *Bifidobacterium longum*, *Parabacteroides spp*., and a decrease in *Alistipes finegoldii* in children with STC compared to healthy children. Parthasarathy and his colleagues found by 16S ribosomal RNA gene sequencing that the colonic mucosal microbiota of STC patients differed from that of healthy patients——increased abundant of *Bacteroidetes spp.* and decreased abundant of *Firmicutes spp*. (*Faecalibacterium, Lactococcus, and Roseburia*). And they revealed that *Firmicutes spp*. were associated with faster colonic transport, and methane (slowing intestinal motility) production was related to the composition of the fecal microbiota but not to constipation or colonic transport[5]. Moreover, the abundance of *Prevotella* is positively correlated with the fiber content of the diet[33]. *Clostridium spp*., and *Ruminococcus spp*. were responsible for the significant fraction of AA, BA and PA production[34]. Our study found that the main types of SCFAs (including AA, BA, CA-1, IBA, IVA, PA and VA) were decreased in the loperamide-induced mice with STC. After being treated by CA, most of SCFAs level were increased with the specific microbiome regulated by CA. The level of BA and VA was significantly increased with *g_UCG.005*, PA was increased with the abundance of *g_Paenalcaligenes* and *g_Psychrobacter* significantly. But the level of CA-1 was significantly decreased with *g__norank_f__Rs-E47_termite_group*.

CONCLUSION

Conclusively, this study provided experimental evidence that CA was an effective agent in treating STC. This conclusion was followed by the results that CA ameliorated the infiltration of neutrophils and lymphocytes, increasing the number of goblet cells and the colon mucosa secretory function. CA significantly improved the diversity and abundance of the beneficial microbiome. Furthermore, the changed abundance of *Firmicutes, Akkermansia, Lachnoclostridium, Monoglobus, UCG.005, Paenalcaligenes, Psychrobacter* and *Acinetobacter* were involved in the production of AA, BA, PA and VA. Our results identified that CA could ameliorate the composition and abundance of the intestinal microbiome to regulate the production of SCFAs in STC.

ARTICLE HIGHLIGHTS

Research background

Slow transit constipation (STC) is a disorder with delayed colonic transit. Cinnamic acid (CA) is an organic acid in natural plants with low toxicity and biological activities to modulate the intestinal microbiome.

Research motivation

We found CA to be very effective in treating STC.

Research objectives
We intend to explore the potential effects of CA on the intestinal microbiome and the primary endogenous metabolites.

Research methods
Loperamide was applied to induce STC in mice. The treatment effects of CA on STC mice were assessed from the 24 *h* defecations, fecal moisture and intestinal transit rate. We used the enzyme-linked immunosorbent assay, Hematoxylin-eosin and Alcian blue and Periodic acid Schiff staining, 16S rDNA and gas chromatography-mass spectrometry to explore the potential effects of CA on the intestinal microbiome and the primary endogenous metabolites-short-chain fatty acids (SCFAs) and evaluate the therapeutic effects of CA in STC.

Research results
CA ameliorated the symptoms and the pathology of STC and treated STC effectively. CA significantly increased the concentration of 5-HT and reduced VIP. CA significantly improved the diversity and abundance of the beneficial microbiome. The production of SCFAs (including acetic acid, butyric acid, propionic acid and valeric acid) was significantly promoted by CA.

Research conclusions
CA could treat STC effectively by ameliorating the composition and abundance of the intestinal microbiome to regulate the production of SCFAs.

Research perspectives
CA is effective in treating STC mice, and further studies are needed to better advance its clinical application.

FOOTNOTES

Author contributions: Jiang JG and Luo Q conceived the project and wrote the manuscript; Luo Q performed the central part of the experiments and analyzed data, with contributions from Li SS, Tan TY, and Xiong K; Yang T and Xiao TB participated in the experimental design and manuscript draft preparation and revision; All authors read and approved the final manuscript.

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MINIREVIEWS

Update on the strategy for intravenous fluid treatment in acute pancreatitis

Thanapon Yaowmaneerat, Apichet Sirinawasatien

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Abstract

Fluid therapy/resuscitation is mandatory in acute pancreatitis due to the pathophysiology of fluid loss as a consequence of the inflammatory process. For many years, without clear evidence, early and aggressive fluid resuscitation with crystalloid solutions (normal saline solution or Ringer lactate solution) was recommended. Recently, many randomized control trials and meta-analyses on fluid therapy have revealed that high fluid rate infusion is associated with increased mortality and severe adverse events compared to those resulting from moderate fluid rates, and this has triggered a paradigm shift in fluid management strategies. Meanwhile, there is evidence to show that Ringer lactate solution is superior to normal saline solutions in this context. The purpose of this review is to provide an update on the strategies for intravenous fluid treatment in acute pancreatitis, including the type, optimal amount, rate of infusion, and monitoring guides. Recommendations from recent guidelines are critically evaluated for this review in order to reach the authors' recommendations based on the available evidence.

Key Words: Acute pancreatitis; Fluid resuscitation; Aggressive fluid resuscitation; Moderate fluid resuscitation; Crystalloids; Colloids

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Core Tip: The standard care for patients with acute pancreatitis is fluid therapy. According to many randomized control trials, early and non-aggressive/moderate fluid resuscitation is preferable to aggressive fluid resuscitation. An excessive amount of fluid resuscitation has been found to cause more vascular leakage, which worsens pancreatic local complications and increases infection and pulmonary complications. Ringer lactate solutions are administered as the fluid of choice in this setting to maintain adequate hemodynamic status, with a mean arterial pressure of ≥ 65 mmHg and urine output of ≥ 0.5 mL/kg/h used as the initial fluid resuscitation goal.

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INTRODUCTION

Acute pancreatitis is an acute inflammatory process of the pancreas with a variable disease course, ranging from mild self-limiting to progressive severe disease resulting in multiple organ failure with high rates of morbidity and mortality. Among patients admitted with acute pancreatitis, around 80% have a mild clinical course; however, the others develop serious illness, with a mortality rate of approximately 20%[1]. No proven pharmacological therapy currently exists to treat acute pancreatitis; however, intravenous (IV) fluid resuscitation is recommended as a fundamental component of initial supportive treatment in order to reduce morbidity and mortality for patients with this condition[2]. Several studies published in the last decade have raised concerns about the efficacy and safety of early aggressive fluid resuscitation in the treatment of acute pancreatitis. Many clinical guidelines for acute pancreatitis recommend vigorous early fluid resuscitation, but over-aggressive fluid therapy can result in poor clinical outcomes, in particular respiratory complications[3] and abdominal compartment syndrome[4]. The objective of this narrative review is to update the most recent evidence on intravenous fluid treatment strategies, as well as to propose the goals of resuscitation and monitoring in patients with acute pancreatitis.

PATHOPHYSIOLOGICAL BASIS

Mortality in severe acute pancreatitis is largely caused by remote organ failure due to activation of excessive pro- and anti-inflammatory mediators and systemic inflammatory response syndrome (SIRS)[5]. Overexpressed inflammatory mediators, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8, will injure the microcirculation endothelium and then increase the permeability of vasculature, resulting in the transudation of fluid from the intravascular to the third space, leading to capillary leakage syndrome and multiple organ dysfunction syndrome[6]. Other consequences of acute pancreatitis are nausea and vomiting with poor intake of adequate amounts of fluids, leading to the intensification of intravascular volume depletion.

In addition, levels of vasoactive mediators and procoagulant factors are increased in acute pancreatitis, probably triggered by inflammatory mediators, promoting capillary vasoconstriction and microthrombi formation[2]. Impaired pancreatic microcirculation *via* increasing capillary permeability, vasospasm, and the formation of microthrombi, have a significant impact on the early stages of the disease and have been implicated as a major contributor to the pathogenesis of pancreatic necrosis[2,6]. Therefore, the goal of effective fluid resuscitation is to restore blood volume deficiency and block the microcirculatory disorder in the early stages of the disease in order to prevent local and systemic complications[6].

Severity grading of acute pancreatitis and risk stratification

The revised Atlanta classification for acute pancreatitis categorizes the disease into two types (interstitial edematous and necrotizing pancreatitis), while the severity is measured on a three-grade scale: Mild (having no local or systemic complications and no organ failure); moderately severe (the presence of local or systemic complications and/or organ failure that resolves within 48 h); and severe (having organ failure that persists for over 48 h)[7]. Interstitial edematous subtypes are usually associated with mild severity, whereas necrotizing pancreatitis is commonly seen in patients with moderately severe or severe acute disease. Three organ systems, the respiratory, kidney, and cardiovascular systems, should be assessed for organ failure based on the modified Marshall scoring system (Table 1)[8]. Mortality in acute pancreatitis occurs early in the course of the disease, and the presence of persistent multi-organ

Table 1 Modified Marshall scoring system for organ dysfunction

	Score[a]				
Organ system	**0**	**1**	**2**	**3**	**4**
Respiration (PaO_2/FiO_2)[b]	> 400	301-400	201-300	101-200	< 101
Kidney (serum creatinine), μmol/L	< 134	134-169	170-310	311-439	> 439
Kidney (serum creatinine), mg/dL	< 1.4	1.4-1.8	1.9-3.6	3.7-4.9	> 4.9
Cardiovascular (systolic blood pressure), mmHg	> 90	< 90, fluid responsive	< 90, not fluid responsive	< 90, pH < 7.3	< 90, pH < 7.2

[a]Score ≥ 2 for any system defines the presence of organ failure.
[b]For nonventilated patients, FiO_2 can be estimated by the rate of supplemental oxygen (Room air, 21%; 2 L/min, 25%; 4 L/min, 30%; 6-8 L/min, 40%; 9-10 L/min, 50%).
FiO_2: Fraction of inspired oxygen; PaO_2: Partial pressure of arterial oxygen.

failure is the key determining factor[9].

Multiple scoring systems have been developed to predict severity and guide management according to the anticipated severity of the disease[10]. Earlier scoring systems, such as the Ranson or Imrie-Glasgow, need to be completed 48 h after admission, which is outside the critical period of the first 12-24 h of hospitalization, where the highest incidence of organ failure occurs[11]. The Acute Physiology and Chronic Health Examination (APACHE) II score, which includes initial values of 12 routine physiologic measurements, including age and chronic health status, was originally developed to predict disease severity and mortality for critically ill patients in intensive care units[12]. It is extensively used in acute pancreatitis to forecast severe disease, with good negative predictive and modest positive predictive values. However, its limitations are that it is complex and cumbersome to use, along with the fact that these variables are not obtained on a regular basis from patients who are not critically ill[13].

The Bedside Index for Severity in Acute Pancreatitis (BISAP) score has been developed to predict in-hospital mortality. The presence of each of the following parameters during the first 24 h is assigned 1 point: Blood urea nitrogen (BUN) > 25 mg/dL; impaired mental status; SIRS; age > 60 years; and the presence of pleural effusion. Patients with a score of 0 have been found to have a mortality rate of < 1%, compared with 22% in those with a score of 5[14]. A cohort of 397 patients found that a BISAP score ≥ 3 was associated with an increased risk of developing organ failure [odds ratio (OR) 7.4, (95%CI: 2.8-19.5)], persistent organ failure (OR 12.7, 95%CI: 4.7-33.9), and pancreatic necrosis (OR 3.8, 95%CI: 1.8-8.5)[15]. In addition, a validation study of the BISAP score which included 185 patients demonstrated that its performance was similar to those of Ranson's, APACHE II, and CT severity index scores in predicting organ failure, complications, and mortality[16]. It is thus widely used because its components are clinically relevant and easily calculated at the bedside.

STRATEGY FOR INTRAVENOUS FLUID TREATMENT

Intravenous hydration or resuscitation is the standard treatment for patients with acute pancreatitis of any severity, to correct hypovolemia and maintain intravascular volume for better tissue perfusion in order to prevent pancreatic microcirculation ischemia and reduce local complications. Fluid hydration needs to be maintained in the early phase to prevent the cascade of events resulting in pancreatic necrosis[2]. A retrospective study found that early fluid resuscitation was associated with a decreased incidence of SIRS and organ failure at 72 h[17]. Hemoconcentration, a marker of hypovolemia, on admission together with persistent 24-hour hemoconcentration, have been found to be associated with the development of necrotizing pancreatitis and organ failure[18]. Many recommendations for fluid replacement are based on observational and retrospective studies conducted since the 1990s which found that it was associated with a reduction in morbidity and mortality[19,20]. At present, there are no clearly defined details of the type, fluid flow rate, total volumes, or goal of resuscitation[21].

Which patient

Fluid replacement is the mainstay treatment recommended for every patient with acute pancreatitis of any severity. It shows benefits in both mild and severe forms of the disease, as confirmed by a single-center randomized controlled trial (RCT) from Buxbaum *et al*[22] of patients with the mild acute pancreatitis, and a study of patients with the severe form by Yamashita *et al*[23]. The latter, which was a multicenter retrospective study of 1097 severe acute pancreatitis patients, revealed that fluid replacement volume > 6 L within the first 24 h was significantly associated with decreased mortality (OR 0.58; $P < 0.05$). However, this treatment may have limitations in patients with underlying disease not included in clinical trials due to the risk of fluid overload. The majority of studies have excluded

patients who had the following: Known history of renal disease (such as those with basal creatinine > 2 mg/dL or who had undergone chronic hemodialysis); greater than the New York Heart Association class II heart failure; chronic lung disease requiring supplemental home oxygen; active acute infection (including acute cholecystitis and acute cholangitis); hypernatremia (serum sodium > 145 mEq/L); hyponatremia (serum sodium < 135 mEq/L); or hyperkalemia (serum potassium > 5 mEq/L)[24]. The patients in this group require individualized assessment and need to be closely monitored[25].

Which fluid

The fluid of choice for rehydration is the isotonic crystalloid solution, which contains normal saline (NS) and balanced/buffered crystalloid [such as lactated Ringer's (LR), Plasma-Lyte, or Hartmann's solution]. NS and LR are most widely used as a first-line solution in acute pancreatitis. The chloride concentration of NS (154 mEq/L) is higher than those of LR (109 mEq/L) and human plasma (94-111 mEq/L)[26]. Infusion of NS generally causes hyperchloremic metabolic acidosis which is dose-dependent[27]. The effect of hyperchloremia on renal function was examined by Chowdhury *et al*[28] who revealed a significant reduction from baseline in mean renal blood flow velocity (P = 0.045) and renal cortical tissue perfusion (P = 0.008) after NS intravenous infusion but not with Plasma-Lyte. Furthermore, chloride load may increase renal inflammation and impair renal perfusion, leading to acute kidney injury and increased risk of renal replacement therapy[28,29].

Regarding clinical evidence of fluid resuscitation using LR and NS, Zhou *et al*[30] performed a meta-analysis of 4 RCTs which made direct comparisons between LR and NS resuscitation in 248 patients, and they found that the LR group was at lower risk of developing moderately severe/severe pancreatitis [OR 0.49, (95%CI: 0.25-0.97)]. In addition, the LR group was less likely than the NS group to require intensive care unit (ICU) admission [OR 0.33, (95%CI: 0.13-0.81)] or develop local complications, defined as a composite of acute peripancreatic fluid collection, pancreatic necrosis, peri-pancreatic necrosis, pancreatic pseudocyst, and walled-off necrosis [OR 0.42, (95%CI: 0.2-0.88]. Meanwhile, there is conflicting evidence regarding whether the use of LR is associated with an anti-inflammatory effect, as shown by the reduction of C-reactive protein levels and incidence of SIRS, as compared with NS[24,31-33].

The recent evidence favoring balanced crystalloids (LR or Plasma-Lyte) over NS is based on two large RCTs that were conducted in 2018. The first by Semler *et al*[29], the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) study of critically ill adults, found that the use of balanced crystalloids for intravenous fluid administration can reduce the composite outcome of in-hospital mortality, new renal replacement therapy, and persistent renal dysfunction compared with the use of NS [(OR 0.90, (95%CI: 0.82–0.99); P = 0.04]. Another study by Self *et al*[26], the Saline Against Lactated Ringer's or plasma-lyTe in the Emergency Department trial, investigated the effect of intravenous crystalloids replacement among noncritically ill patients in the emergency department who were subsequently hospitalized outside an ICU. This study revealed that, compared with NS, the balanced crystalloids resulted in a lower incidence of major adverse kidney events within 30 days [4.7% *vs* 5.6%; adjusted OR 0.82, (95%CI: 0.70-0.95); P = 0.01].

The use of colloids should be avoided given the absence of demonstrable benefits in terms of decreased mortality and possible increased risk of organ failure[6,34]. The colloid solutions can be divided into two groups: 'semi-synthetic' [hydroxyethyl starch (HES), gelatin, and dextran solutions]; and 'natural' (human albumin solution). Colloids are IV fluids that contain high molecular weight, microscopic substances suspended in crystalloid solutions which have the theoretical ability to stay in the intravascular space longer than crystalloids due to oncotic pressure from macromolecules in solution. HES is the most frequently used colloid, and a small RCT by Xiao *et al*[35] showed that resuscitation with HES compared to LR can decrease the risk of intra-abdominal hypertension and reduce the need for mechanical ventilation in severe acute pancreatitis patients. The data from a large RCT comparing HES with NS resuscitation in 7000 patients in the ICU, revealed no survival benefit of HES and found that it actually resulted in increased use of renal replacement therapy [RR 1.21, (95%CI: 1.00-1.45); P = 0.04][36]. A recent meta-analysis by Di Martino *et al*[37] found that in comparison with the use of HES, NS reduced the number of severe adverse events [RR 0.38, (95%CI: 0.27-0.54); P < 0.001] and organ failure [RR 0.30, (95%CI: 0.21-0.44); P < 0.001][37]. Human serum albumin infusion, a common fluid given to acute pancreatitis patients admitted to the ICU, has no proven benefits. A recent large retrospective cohort study comparing patients who received human serum albumin infusion (n = 228) to those who did not (n = 772) found that it did not reduce in-hospital mortality and was, in fact, associated with longer hospital and ICU stays. The study also revealed that the outcome was unaffected by initial serum albumin levels, infections, or total amount or initial timing of infusion[38].

As a result, we opted for LR as the first choice for fluid therapy over NS, agreeing with many other guidelines in recommending against the use of HES for IV resuscitation in patients with acute pancreatitis[34,39].

Rate and volume

While early and aggressive fluid resuscitation has been discussed in many studies in the literature and is recommended by many guidelines[19,40], the optimal volumes and rates of fluid replacement are still unknown. To date, the early resuscitation period has been reduced to a 4-6 h therapeutic window from

the initial hospital presentation. Evidence from a large multicenter retrospective study by Singh *et al*[41] demonstrated that early fluid resuscitation > 1 L in the first 4 h compared with < 0.5 Liter in the first 4 h was associated with a significantly lower need for interventions. It has been estimated that fluid sequestration in the first 48 h is 3.7 L in mild pancreatitis and 5.6 L in severe pancreatitis[42]. In addition, baseline predictors for a higher volume of fluid sequestration have been found to be younger age, high hematocrit, high blood glucose, SIRS ≥ 2, and history of excessive alcohol consumption, and it has been suggested that these factors can help to identify patients who need more aggressive fluid resuscitation[43].

The first RCT to analyze the optimal fluid therapy issue was conducted by Mao *et al*[44] in 2009, and they found that aggressive fluid resuscitation (rate 10-15 mL/kg/h *vs* 5-10 mL/kg/h) increased mortality and complications, including respiratory failure, abdominal compartment syndrome, and sepsis. Subsequently, many RCTs have been conducted with reduced rates of IV fluid, but these studies revealed no benefit of aggressive IV hydration and have instead identified its harmful effects, as shown in Table 2. A recent meta-analysis by Di Martino *et al*[37] included 4 RCTs that compared aggressive rate *vs* moderate rate of resuscitation and found that, compared with moderate fluid rate infusion, high fluid rate infusion was associated with increased mortality [OR 2.88, (95%CI: 1.41-5.88); P = 0.004], higher numbers of severe adverse events [RR 1.42, (95%CI: 1.04-1.93); P = 0.030], and increased incidence of sepsis [RR 2.80, (95%CI: 1.51-5.19); P = 0.001].

Specifically investigating patients with mild pancreatitis, a previous RCT conducted by Buxbaum *et al*[22] showed that aggressive fluid hydration appeared to be effective. However, a recent large RCT, the WATERFALL study, in which 249 patients with mild pancreatitis were included in the interim analysis, was conducted to compare aggressive (bolus 20 mL/kg, then infusion 3 mL/kg/h) and moderate (preceded by bolus 10 mL/kg only if the patient had hypovolemia, then infusion 1.5 mL/kg/h) fluid resuscitation. The median volume of fluid given during the first 48-h period was higher in the aggressive-resuscitation group than in the moderate-resuscitation group (7.8 *vs* 5.5 L). The study terminated early owing to safety issues regarding whether aggressive fluid resuscitation was harmful, as it resulted in a higher incidence of fluid overload (20.5%) in the aggressive-resuscitation group compared with 6.3% in the moderate-resuscitation group, adjusted [RR 2.85; (95%CI: 1.36-5.94), P = 0.004], while no statistical significance was observed in the development of moderately severe or severe pancreatitis during hospitalization[47].

In the absence of conclusive high-quality evidence, society guidelines have recommended various fluid resuscitation approaches for acute pancreatitis. Many guidelines recommend early aggressive fluid therapy without providing full details[19,40]. The American College of Gastroenterology (ACG) recommended the use of an aggressive hydration rate of 250-500 mL/h in the first 12-24 h[48]. Japanese guidelines issued in 2015 recommended short-term rapid fluid resuscitation for patients in shock or with dehydration (150-600 mL/h depending on the hemodynamics status) during the early stages of acute pancreatitis, while 130-150 mL/h of optimal fluid infusion rate was advised for those without dehydration[25]. Although the revised Japanese guidelines of 2021 recommended aggressive fluid resuscitation as initial therapy, they omitted information on the rate at which the fluids should be administered[40]. On the other hand, utilizing "goal-directed" fluid resuscitation has been advised by both the American Gastroenterological Association[34] and the International Association of Pancreatology/American Pancreatic Association (IAP/APA)[39]. Additionally, a starting IV rate of 5-10 mL/kg/h has been suggested until resuscitation goals have been met[39].

Based on the available evidence, we recommend a moderate fluid resuscitation strategy, beginning with LR IV rate of 1.5 mL/kg/h in the first 24-48 h, preceded by a bolus of 10-20 mL/kg in 1-2 h if patients have moderately severe to severe pancreatitis, hypovolemia, signs of dehydration, acute kidney injury, or poor predictive indicators, such as BUN > 25 mg/dL or hematocrit ≥ 44%(Table 3).

Goal and monitoring

The goal of fluid resuscitation is to correct hypovolemia and improve organ and tissue perfusion by increasing intravascular volume in order to increase cardiac output and reduce complications[27,49]. Response to fluid resuscitation depends on cardiac function, baseline preload, and duration of intravascular volume expansion. In critically ill patients, especially those with sepsis, severe trauma, or acute pancreatitis, the inflammatory process and cytokines damage the endothelial glycocalyx leading to alterations in vascular permeability resulting in increased capillary leakage and loss of albumin. It triggers increased rates of fluid loss from the intravascular to the extravascular space, which causes depletion in intravascular volume, so that a bolus dose or maintenance of fluid hydration is needed[27]. Accordingly, volume status requires interval assessment to balance the risk of volume overload against the risk of hypovolemia from fluid leakage, insensible loss, poor intake, and vomiting, particularly in severe pancreatitis[50,51].

Goal-directed fluid treatment, which is defined as the use of several parameters and perfusion targets to guide the titration of fluid administration, has been used in multiple studies and guidelines as a key concept[34,39], and it has been shown to improve survival rates in patients with sepsis and septic shock [52]. Four RCTs with various fluid administration methods used goal-directed therapy for acute pancreatitis, but no obvious benefit was revealed[34]. Another study, however, suggested that goal-directed fluid treatment may be associated with increased survival. Wang *et al*[53] conducted a prospective study

Table 2 Summary of randomized controlled trials comparing different intravenous fluid resuscitation strategies in acute pancreatitis

Ref.	Design	N	Participants	Randomization	Aggressive resuscitation	Volume	Nonaggressive resuscitation	Volume	Effect of early aggressive resuscitation
Mao *et al* [44], 2009	Superiority	76	Severe AP	72 h	Rapid volume expansion (10-15 ml/kg/h)	4 ± 2 L Crystalloid; 1.3 ± 0.8 L; Colloid in 24 h	Controlled volume expansion (5-10 ml/kg/h)	2.4 ± 1.9 L Crystalloid; 0.9 ± 0.6 L; Colloid in 24 h	Harmful, more sepsis, mortality, mechanical ventilation, and ACS
Mao *et al* [46], 2010	Superiority	115	Severe AP	24 h	Rapid hemodilution with goal Hct < 35% at 48 h	-	Slow hemodilution with goal Hct > 35% at 48 h	-	Harmful, more sepsis, and mortality
Wu *et al*[31], 2011	Factorial	40	Any severity	6 h	Goal-directed with 20 ml/kg bolus + 3 or 1.5 ml/kg/h of LR or NS	4.3 L in 24h	LR or NS fluid therapy adjusted by treating physician	4.6 L in 24h	Similar, SIRS, and CRP at 24 h
Buxbaum *et al*[22], 2017	Superiority	60	Predicted mild AP	4 h	20 ml/kg bolus + 3 ml/kg/h of LR	5.6 L in 24 h; 7.6 L in 36 h	10 ml/kg bolus then 1.5 ml/kg/h of LR	3.9 L in 24 h; 5.6 L in 36 h	Beneficial, less composite outcome, SIRS, and hemoconcentration
Cuéllar-Monterrubio JE *et al*[45], 2020	Two-tailed	88	Any severity AP, more than 24 hr disease onset	4 h	20 mL/kg bolus + 3 mL/kg/hr first 24 hours and then 30 mL/kg for the next 24 hours	8.54 ± 1.83 L in 48 h	20 ml/kg bolus (if hypovolemia, 3/45) - 1.5 ml/kg/h of HS first 24 hours and then 30 mL/kg for the next 24 hours	5.13 ± 1.28 L in 48 h	No benefit, no differences found in SIRS, pancreatic necrosis, Respiratory complication, AKI, and LOS
De-Madaria E *et al*[47], 2022	Two-tailed	249	Mild AP, less than 24 h disease onset	8 h	20 ml/kg bolus + 3 ml/kg/h of LR	7.8 (6.5-9.8) L in 48h	10 mL/kg bolus (if hypovolumia) - 1.5 ml/kg/h of LR	5.5 (4.0-6.8) L in 48 h	Harmful, more fluid overload

AP: Acute pancreatitis; ACS: Abdominal compartment syndrome; LR: Lactated Ringer's; NS: Normal saline; SIRS: Systemic inflammatory response syndrome; CRP: C-reactive protein; HS: Hartmann's solution; AKI: Acute kidney injury; LOS: Length of stay.

using the goal-directed objectives of fluid resuscitation during the first 6 h of severe acute pancreatitis individuals who were admitted to the ICU within 24 h of the onset of the disease. Objectives should include all of the following: central venous pressure (CVP) 8-12 mmHg; mean arterial pressure (MAP) ≥ 65 mmHg; urine output ≥ 0.5 mL/kg/h; and central venous (superior vena cava) or mixed venous oxygen saturation ≥ 70%. The study showed that goal-directed therapy reduced mortality in patients with severe acute pancreatitis[53].

Laboratory tests for determining volume status and sufficient tissue perfusion include measuring hematocrit, BUN, creatinine (Cr), and lactate[19]. Acute renal injury is caused by reduction of intravascular volume together with a direct renal injury mechanism occurring in acute pancreatitis, which is facilitated by the leak of activated enzymes such as trypsin and chymotrypsin, inflammatory mediators, and cytokines; these are the reasons for increased BUN in acute pancreatitis patients[54]. An elevated BUN has been used as a marker of severe disease, whereas a declining BUN indicates improving renal perfusion and adequate resuscitation; therefore, the point at which the BUN level decreases or is normalized is used as the endpoint of a goal-directed fluid resuscitation protocol[31].

Hematocrit has long been used to guide fluid replacement in critically ill patients, and it has also been identified as a marker that correlates with the development of pancreatic necrosis in acute pancreatitis [18,55]. Brown *et al*[56] previously demonstrated that hemoconcentration, with a hematocrit of ≥ 44% on admission or failure of hematocrit to decrease at 24 h, was associated with the development of necrotizing pancreatitis[56]. A recent retrospective study from a prospective database of 628 patients also found that hemoconcentration at baseline or an increase in hematocrit at 24 h was associated with persistent organ failure (OR = 2, P = 0.03)[57].

Elevated serum lactate should be considered as a factor for guidance in the treatment of critically ill patients, since it is well-recognized as a marker of tissue hypoxia/hypoperfusion, as well as a marker of resuscitation in the setting of unstable hemodynamics, and it should be monitored[19], although there is no evidence to support its relevance in patients with acute pancreatitis. Unfortunately, other serum biomarkers, such as brain natriuretic peptide, neutrophil gelatinase-associated lipocalin (NGAL), and intestinal fatty acid-binding protein (I-FABP), fail to differentiate between fluid responsive and

Table 3 Authors' recommendations for fluid resuscitation strategy in acute pancreatitis

Parameter	Recommendation
Who	All patients with any severity
Timing	Early fluid resuscitation is better
Type of fluid	Ringer lactate solutions better than normal saline solutions
	Avoid synthetic colloids (HES or Dextran), Limited data in human albumin
Amount of fluid	
Mild pancreatitis	3 L in 24 h and 4-6 L in 48 h
Moderate or severe pancreatitis	3-4 L in 24 h and 6-8 L in 48 h based on clinical/lab parameters
Rate of infusion	
Mild pancreatitis	1.5 mL/kg/h with bolus dose 10 mL/kg/h in 1-2 h in patients with hypovolemia, BUN > 25, Hematocrit ≥ 44%, AKI, Age < 40 yr, and Alcoholic etiology
Moderate or severe pancreatitis	1.5-3 mL/kg/h with bolus dose 10-20 mL/kg/h in 1-2 hours or higher in hypotension
Monitoring goals	MAP ≥ 65 mmHg, Urine output ≥ 0.5 mL/kg/h
	Hematocrit < 44% and/or BUN < 25 mg/dL at 12 and 24 h (for guided fluid rate adjustment)
	Invasive monitoring and dynamic parameters needed in ICU patients or cardio/renal dysfunction patients
Duration	24-48 h, Infusion can stop after 24 h if oral feeding can be tolerated in mild pancreatitis

HES: Hydroxyethyl starch; BUN: Blood urea nitrogen; AKI: Acute kidney injury; MAP: Mean arterial pressure.

refractory patients[49].

In cases of severe pancreatitis with organ failure in the ICU, when fluid restriction is warranted due to renal or cardiac dysfunction, an invasive clinical assessment is required. A single clinical sign or non-invasive clinical assessment cannot accurately reflect volume status, and the use of multiple parameters measured by an invasive technique is more reliable[58]. CVP is a traditional static parameter that is often used in general practice in order to indicate volume status and preload responsiveness[59]. However, in severe pancreatitis, it may not be as good a parameter as septic shock, since massive fluid extravasation (pleural effusion, ascites), frequently leads to falsely high CVP values from increased intrathoracic and intraabdominal pressure, resulting in under-resuscitation when employing CVP-based algorithms[60].

Dynamic parameters and tests (*e.g.*, passive leg raising test) that measure cardiac response with changes in preload, such as stroke volume variation and pulse pressure variation, are better predictors of volume status and fluid responsiveness. A pilot study was recently conducted by Jin *et al*[61] to evaluate a strategy for optimizing fluid requirements following initial resuscitation in individuals with predicted severe acute pancreatitis. It was designed for serial monitoring of an objective clinical assessment of volume status (heart rate, mean arterial pressure, urine output, and hematocrit), and to measure the changes in stroke volume in response to a mini-fluid challenge (250 mL over 10 min) and the passive leg-raising test. They found that a mini-fluid challenge and the resulting change in stroke volume can be used as the goal to determine the rate of IV fluid therapy (5-10 *vs* 1-3 mL/kg/h). Additionally, the passive leg-raising test was superior to an objective clinical assessment of volume status for predicting fluid responsiveness and guiding fluid therapy, and it is therefore noteworthy of further study in this regard[61].

According to the IAP/APA 2013 guidelines for the management of acute pancreatitis, the aim of fluid resuscitation should be based on one or more of the following: (1) Non-invasive clinical targets (heart rate < 120/min, mean arterial pressure 65-85 mmHg, and urinary output > 0.5-1 mL/kg/h; (2) Invasive clinical targets of stroke volume variation, and intrathoracic blood volume determination; and (3) Biochemical targets of hematocrit 35%-44%[39]. Meanwhile, Japanese guidelines of 2015 recommended that after rapid fluid resuscitation, until MAP ≥ 65 mmHg and urine output ≥ 0.5 mL/kg/h are reached, IV fluid should be given at a slower rate and adjusted to maintain these targets. These guidelines also stated that decreases in BUN, hematocrit, and CVP did not serve as useful indicators for discontinuation of fluid resuscitation[25]. Evidence from nationwide surveys in Japan in 2011 and 2016, showed that compliance with acute pancreatitis bundles for the early management (within the first 48 h) of patients with severe acute pancreatitis, using a MAP ≥ 65 mmHg and a urine output ≥ 0.5 mL/kg/h as adequate resuscitation targets, can improve patient survival rates[62-64].

We recommend using a MAP ≥ 65 mmHg and a urine output ≥ 0.5 mL/kg/h as a goal for the initial phase of fluid resuscitation based on the available data. An interval clinical assessment to check for signs of dehydration/volume overload and to maintain MAP ≥ 65mmHg and urinary output ≥ 0.5 mL/kg/h is essential. Fluid rate adjustments during the maintenance phase should be guided by the biochemical targets of hematocrit of 35%-44% at 12 and 24 h after disease onset (Table 3).

CONCLUSION

Fluid therapy/resuscitation is currently the mainstay treatment for acute pancreatitis. Non-aggressive fluid resuscitation is a new paradigm shift in fluid management that is recommended and should be considered. The preferred fluid is the Ringer lactate solution, with MAP ≥ 65 mmHg and urine output ≥ 0.5 mL/kg/h as the initial fluid resuscitation goal. There is still insufficient evidence to establish the best strategy for fluid optimization after initial resuscitation in patients who have severe pancreatitis or who require fluid restriction due to cardio or renal dysfunction. While hemoconcentration is a poor predictor, serial hematocrit can guide fluid adjustment by maintaining a target hematocrit of < 44%.

FOOTNOTES

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CASE REPORT

Hepatitis C virus treatment with glecaprevir and pibrentasvir in patients co-prescribed carbamazepine: Three case reports

Michael Braude, Dilip T Ratnam, Louise Marsh, Joshua H Abasszade, Anouk T Dev

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Abstract

BACKGROUND

Highly effective and well-tolerated direct-acting antiviral (DAA) therapies have revolutionised the management of hepatitis C virus (HCV); however, niche populations face treatment barriers. DAAs co-prescribed with several first-generation anti-epileptic drugs (AEDs) are contraindicated due to drug-drug interactions. A common example is carbamazepine whereby steady-state carbamazepine reduces the maximum concentration and area under the curve of velpatasvir, glecaprevir and pibrentasvir due to potent cytochrome P450 (CYP) 3A4 induction. Carbamazepine also induces P-glycoprotein which reduces glecaprevir and pibrentasvir's area under curve to infinite time. Sofosbuvir-velpatasvir and glecaprevir-pibrentasvir are contraindicated in patients who are co-prescribed carbamazepine due to the risk of reduced DAA therapeutic effect and consequently, virological treatment failure. This presents a challenge for patients in whom carbamazepine substitution is medically unfeasible, impractical or unacceptable. However, the properties of current generation DAA therapies, including high-potency non-structural protein 5A inhibitory effect, may be sufficient to overcome reduced bioavailability arising from carbamazepine related CYP 3A4 and P-glycoprotein induction.

CASE SUMMARY

We present a case series of three patients with non-cirrhotic, treatment-naïve, genotype 1a, 1b, and 3a HCV who were treated with a 12 wk course of glecaprevir-pibrentasvir, while co-prescribed carbamazepine for seizure disorders. Glecaprevir-pibrentasvir combination therapy was chosen due to its potent *in vitro* activity and low barrier to pan-genotypic resistance associated variants. DAA therapy was dose-separated from carbamazepine to maximise time to peak concentration, and taken with meals to improve absorption. Sustained virological

response at 12 wk was achieved in each patient with no adverse outcomes.

CONCLUSION
DAA therapies, including glecaprevir-pibrentasvir, warrant consideration as a therapeutic agent in people with HCV who are co-prescribed carbamazepine, particularly if AED substitution is not feasible.

Key Words: Antiepileptic drugs; Drug interactions; Hepatitis C virus; Sustained virological response; Health care access; Case report

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Core Tip: Current hepatitis C virus (HCV) direct-acting antiviral (DAA) therapies are not recommended in patients who are co-prescribed carbamazepine. For glecaprevir-pibrentasvir, this is primarily due to carbamazepine's potent induction of cytochrome P450 3A4 and P-glycoprotein which reduces DAA plasma concentration and may therefore lead to virological failure. Despite theoretical reduction in DAA bioavailability, glecaprevir-pibrentasvir, prescribed over 12-wk, may be an effective treatment for non-cirrhotic patients with HCV who are co-prescribed carbamazepine. Glecaprevir-pibrentasvir should be considered for management of HCV in non-cirrhotic patients who are unable to substitute carbamazepine therapy. Further pharmacokinetic and potency data are required, in addition to further data in patients with cirrhosis.

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INTRODUCTION

Highly effective and well tolerated direct-acting antiviral (DAA) therapies have revolutionised the management of hepatitis C virus (HCV). Despite this, multiple barriers to HCV elimination exist, including niche drug-drug interactions. One such example pertains to carbamazepine. Carbamazepine is an anti-epileptic drug (AED) which is commonly prescribed for management of epilepsy, including stabilised and difficult-to-manage cases. Carbamazepine may also be prescribed for management of bipolar affective disorder and neuropathic disorders[1,2]. Neither sofosbuvir/velpatasvir or glecaprevir-pibrentasvir is recommended in patients treated with carbamazepine[3]. This is reflected in the product information statements for sofosbuvir/velpatasvir and glecaprevir-pibrentasvir (last revised July 2021 and November 2021, respectively). The reason for this recommendation is based on evidence that carbamazepine induces both cytochrome P450 (CYP) 3A4 and intestinal P-glycoprotein (P-gp). Induction of these pathways can reduce DAA bioavailability, thereby increasing the risk of HCV treatment failure. Importantly, neither sofosbuvir/velpatasvir or glecaprevir-pibrentasvir significantly impacts the bioavailability or efficacy of carbamazepine[4].

CYP 3A4 induction reduces the maximum concentration of glecaprevir, pibrentasvir and velpatasvir by approximately two-thirds and the area under the curve by one-half[5]. Induction of P-gp by carbamazepine additionally effects glecaprevir and pibrentasvir metabolism. In a phase one, healthy human study, Kosloski *et al*[4] attributed carbamazepine P-gp induction to a 66% and 51% reduction in area under curve to infinite time of glecaprevir and pibrentasvir. Furthermore, sofosbuvir's intestinal absorption (but not the active metabolite, GS-331007)[6] may be halved by induction of intestinal P-gp[7]. This does not appear to be significant at carbamazepine doses of less than or equal to 400 mg/d[7]; however, patients on higher doses of carbamazepine have been successfully treated for HCV without sofosbuvir dose adjustment[8].

There are emerging clinical data which demonstrate successful HCV treatment using DAAs in patients co-prescribed carbamazepine. van Seyen *et al*[8] described four carbamazepine-treated patients with HCV who achieved sustained viral response after 12 wk of treatment (SVR12) with sofosbuvir (400 mg daily) plus dose-escalated daclatasvir (90 mg daily, 60 mg twice daily, or 60 mg three times daily) ± ribavirin. Three of the patients, one of whom was cirrhotic, were managed with a daily carbamazepine dose of greater than or equal to 1000 mg. A retrospective audit by Natali *et al*[9] described a non-cirrhotic patient with genotype 1a HCV on carbamazepine who was successfully treated with an 8 wk course of glecaprevir-pibrentasvir. Data pertaining to DAAs in patients co-prescribed with carbamazepine analogues are also emerging. Sofusbuvir together with dose-escalated daclatasvir has been shown to successfully treat a patient co-prescribed oxcarbazepine[6]. Recently, Marcos-Fosch *et al*[10], reported a case series which included four patients with non-cirrhotic HCV who were successfully treated with DAAs whilst co-prescribed oxcarbazepine and eslicarbazepine. Two of the patients were treated with an 8 wk course of glecaprevir-pibrentasvir (genotypes 1b and 3), another with sofosbuvir-ledipasvir (genotype 1b), and the fourth with 12 wk of sofosbuvir-velpatasvir.

In this case series, we report glecaprevir-pibrentasvir HCV treatment in three patients with non-cirrhotic, treatment-naïve HCV, in whom AED substitution was either not tolerated or accepted. This case series adds to the relative paucity of literature supporting the use of DAA therapies in people with co-prescribed carbamazepine.

CASE PRESENTATION

Chief complaints

Case 1: A 43-year-old lady with genotype 1b, non-cirrhotic HCV required antiviral therapy. However, she was on carbamazepine which is contraindicated with DAA therapy.

Case 2: A 72-year-old man with long-standing genotype 1a, non-cirrhotic HCV required antiviral therapy. He was on carbamazepine which is contraindicated with DAA therapy.

Case 3: A 52-year-old lady presented to her general practitioner for management of treatment-naïve, non-cirrhotic genotype 3a HCV. She was on carbamazepine which is contraindicated with DAA therapies.

History of present illness

Case 1: The patient had medically acquired, treatment-naive, non-cirrhotic genotype 1b HCV. She was a long-term patient in our hepatology clinic.

Case 2: The patient had been monitored in our hepatology clinic for 10-years, but had remained untreated for HCV due co-prescribed carbamazepine. He had stable, non-cirrhotic liver disease.

Case 3: The patient, who had been diagnosed with HCV, lived in a regional area, 250 kilometres from the nearest tertiary medical centre, and received all medical care from her primary care practitioner.

History of past illness

Case 1: The patient was managed with 300 mg twice daily immediate-release carbamazepine for secondary seizure disorder following a childhood intracranial haemorrhage in the setting of congenital factor VIII deficiency.

Case 2: The patient had been managed with immediate-release carbamazepine, 200 mg twice daily for nocturnal seizures. He had been seizure-free for 20 years. Substitution to an alternative AED had been discussed with the patient. However, AED substitution would have required a 12-wk driving moratorium. The patient declined this as he was the primary carer for his partner, and given their remote geographic living situation, required his car to attend medical appointments and other care responsibilities.

Case 3: The patient was managed with 400 mg/600 mg twice daily carbamazepine for generalised seizure disorder. She had been seizure-free for many years and did not wish to trial AED substitution to facilitate DAA therapy.

Personal and family history

Case 1: She had no additional personal or relevant family history.

Case 2: He had a history of dyslipidaemia, hypertension, and depression. Other medications included rosuvastatin and fluoxetine. There was no relevant family history.

Case 3: She had no additional relevant personal or family history.

Physical examination

Three patients had no signs or features of chronic liver disease, nor any extrahepatic manifestations of HCV.

Laboratory examinations

Case 1: The patient's pre-treatment viral load was $\log_{10}$ 5.21 IU/mL.

Case 2: The patient's pre-treatment viral load was $\log_{10}$ 6.81 IU/mL. His pre-treatment alanine aminotransferase was 31 U/L (< 35).

Case 3: The patient's pre-treatment viral load was $\log_{10}$ 6.1 IU/mL. The aspartate aminotransferase to platelet ratio index was 0.21, indicating a high negative predictive value for ruling out cirrhosis.

Imaging examinations

Case 1: The patient was non-cirrhotic based on ultrasonography. The liver stiffness was 2.3 kPa on Fibroscan, which confers a high negative predictive value for ruling out cirrhosis.

Case 2: The patient had no sonographic features of cirrhosis. The liver stiffness was 5.9 kPa on Fibroscan, with a high negative predictive value for ruling out cirrhosis.

Case 3: The patient was non-cirrhotic based on ultrasonography.

MULTIDISCIPLINARY EXPERT CONSULTATION

Case 1: When DAA therapies became available a decision was made to substitute carbamazepine to levetiracetam to facilitate HCV treatment. Levetiracetam 500 mg twice a day was commenced with a plan to wean carbamazepine by 200 mg per week. However, the patient experienced seizure recurrence within two weeks of carbamazepine withdrawal. Alternative AED substitution strategies were declined by the patient. A discussion between the hepatology, pharmacy and neurology teams was coordinated. The recommendation was to consider co-prescribed glecaprevir-pibrentasvir without adjusting the patient's carbamazepine therapy.

Case 2: Careful consideration was given to this case, and given the patient's situation, a recommendation was made to trial co-prescribed glecaprevir-pibrentasvir without changing the patient's carbamazepine therapy. This followed a discussion between our hepatology and pharmacy teams, as well as a risk *vs* benefit discussion with the patient.

Case 3: The medical practitioner prescribed glecaprevir-pibrentasvir treatment together with co-prescribed carbamazepine following a risk *vs* benefit discussion with the patient. The case was subsequently discussed with a tertiary health centre given our experience with previous similar cases. Based on further discussion, glecaprevir-pibrentasvir treatment was extended to a 12 wk course and was dose-separated from carbamazepine.

FINAL DIAGNOSIS

Case 1: HCV with reduced treatment options due to contraindication of carbamazepine with co-prescribed DAA therapies, and seizure recurrence with AED substitution therapy.

Case 2: HCV with reduced treatment options due to contraindication of carbamazepine with co-prescribed DAA therapies, and inability to substitute AED therapy due to extenuating social factors.

Case 3: HCV with reduced treatment options due to contraindication of carbamazepine with co-prescribed DAA therapies, and patient preference to avoid AED substitution.

TREATMENT

Case 1: Several years after the initial attempt at AED substitution, a decision was made to prescribe a 12 wk course of glecaprevir-pibrentasvir without changing the patient's carbamazepine therapy. DAA therapy was administered with food and was taken between morning (07:00) and evening (19:00) carbamazepine doses.

Case 2 and case 3: The patient accepted and completed treatment with 12-wk of glecaprevir-pibrentasvir, dose-separated from carbamazepine.

OUTCOME AND FOLLOW-UP

Case 1: The patient's HCV viral load was log 1.61 IU/mL by week four of DAA therapy. The HCV viral load was undetectable at the end of treatment (EOT) and remained undetectable 12-wk following the EOT. No treatment adverse effects were reported. The carbamazepine level remained unchanged at 28 μmol/L (range 17-51 μmol/L) at the EOT. The patient was subsequently discharged back to her primary care practitioner (Table 1).

Case 2: HCV viral load was undetectable at four weeks, eight weeks, EOT, and at 12 wk post treatment. There were no adverse drug reactions and the patient was discharged from hepatology follow-up (Table 1).

Case 3: DAA treatment was well-tolerated and HCV viral load was undetectable at the EOT and at 12 wk post treatment (Table 1).

DISCUSSION

Drug-drug interactions remain an issue in the management of HCV[11], particularly in circumstances where substitution therapy or drug holidays are not feasible, practical or acceptable. However, current DAA therapies are highly potent and evidence is accumulating that SVR12 can be achieved despite carbamazepine induced reduction in DAA bioavailability[6, 8-10].

We report HCV SVR12 with glecaprevir-pibrentasvir in three non-cirrhotic patients who were managed with carbamazepine for seizure disorders. We chose pibrentasvir over a velpatasvir-containing regimen due to its potent *in vitro* activity against pan-genotypic resistance associated variants, including Y93H, which may confer resistance to other non-structural protein 5A inhibitors[12,13]. We acknowledge that sofosbuvir-based regimens may also be beneficial given the limited metabolism of GS-331007 by carbamazepine[6].

Table 1 Overview of 3 patients treated with a 12-wk course of carbamazepine whilst co-prescribed carbamazepine for seizure disorders

Patient	Age	Gender	HCV genotype	Treatment-experienced	Cirrhotic	CBZ dose	SVR12
1	43	Female	1b	No	No	300 mg BD	Yes
2	72	Male	1a	No	No	200 mg BD	Yes
3	52	Female	3a	No	No	400/600 mg BD	Yes

HCV: Hepatitis C virus; CBZ: Carbamazepine; SVR 12: Sustained virological response at 12-wk.

Our treatment strategy relied on a triad of: (1) Dose-separating glecaprevir-pibrentasvir from carbamazepine; (2) Administering glecaprevir-pibrentasvir with food; and (3) Treatment extension of glecaprevir-pibrentasvir to 12 wk. To outline each of these in turn, dose separation was hypothesised to optimise first pass bioavailability of glecaprevir and pibrentasvir. This is because glecaprevir and pibrentasvir each has a time to peak concentration of five hours, which is similar to that of immediate-release carbamazepine. Dose-separation of carbamazepine and DAA therapy may result in greater peak DAA bioavailability. The absolute benefit of this is not known given that the area under the curve for minimum effective concentration of carbamazepine is in the order of 12-17 h and would therefore overlap with dose separated DAA therapy. In addition to dose separation, we recommended co-administration of DAA therapy with food to enhance glecaprevir-pibrentasvir absorption. Finally, we recommended DAA treatment extension to bolster suppression of HCV viral replication.

A limitation of this study is the small sample size. Our findings are however, mirrored by other small case series, as outlined previously. Another limitation is that we did not monitor drug levels during treatment. The decision against on-treatment drug monitoring was made due to: (1) The excellent *in vivo* potency of glecaprevir-pibrentasvir[14]; (2) The availability of salvage therapies; and (3) The minimal effect of glecaprevir-pibrentasvir on carbamazepine metabolism[4]. We suggest that on-treatment DAA levels and viral titres may not be requisites in treatment-naïve, non-cirrhotic patients, but should be considered in people with previous treatment failure and/or compensated cirrhosis until further data are available.

CONCLUSION

Glecaprevir-pibrentasvir over a 12 wk course administered with food appears to overcome reduced DAA plasma concentrations resulting from carbamazepine-related CYP 3A4 and P-gp induction. This treatment regimen should be considered in non-cirrhotic HCV in whom carbamazepine substitution, or a drug holiday is not possible, particularly given the potency of pibrentasvir and low likelihood of pan-genotypic resistance associated variants. Further pharmacokinetic and controlled studies are required to bolster this contention. Until further data are available, close on-treatment monitoring should be provided with specialist involvement.

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ORIGINAL ARTICLE

Case Control Study

Effectiveness of an amino acid beverage formulation in diarrhea-predominant irritable bowel syndrome: A pragmatic real-world study

Samantha E Niles, Phil Blazy, Samuel N Cheuvront, Robert W Kenefick, Sadasivan Vidyasagar, Adam B Smith, Neil Fawkes, William Denman

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Abstract

BACKGROUND

Amino-acid based medical foods have shown promise in alleviating symptoms of drug induced gastrointestinal side effects; particularly, diarrhea-predominant symptoms. Irritable bowel syndrome (IBS) is a gastrointestinal disorder that affects up to 9% of people globally, with diarrhea predominant IBS (IBS-D) being the most prevalent subtype. Further trials are needed to explore potential added benefits when integrated into standard care for IBS-D.

AIM

To assess the effectiveness of an amino acid-based medical food as an adjunct to standard of care for adults with IBS-D.

METHODS

This is a pragmatic, real world, open label, single arm study comparing a 2-week baseline assessment to a 2-week intervention period. One hundred adults, aged 18 to 65 years, with IBS-D, according to Rome IV criteria, were enrolled after completing a 2-week baseline assessment period and received a 2-week supply of an amino acid based medical food which was consumed at home twice daily on top of their standard of care. The primary outcome was an assessment of tolerability after 2-weeks of consumption, while secondary outcomes included changes in stool consistency (Bristol Stool Form Scale), severity of abdominal pain & discomfort, symptoms of urgency, Global Improvement Survey (GIS), and the IBS

severity scoring system (IBS-SSS).

RESULTS

The test product was well-tolerated as each participant successfully completed the full 14-day trial, and there were no instances of dropouts or discontinuation of the study product reported. Forty percent of participants achieved a 50% or more reduction in the number of days with type 6-7 bowel movements (IBS-D stool consistency responders). Fifty-three percent of participants achieved a clinically meaningful reduction of 30% in mean weekly pain scores, and 55% experienced the same for mean weekly discomfort scores (IBS-D pain and discomfort responders). Participants experienced a mean -109.4 (95% confidence interval: -130.1, -88.8) point reduction on the IBS-SSS and 52% experienced a minimally clinically important difference of > 95 points. An IBS-SSS category shift from severe to moderate or mild occurred in 69% of participants. For functional symptoms, 76% of participants reported symptom relief on the GIS.

CONCLUSION

The amino acid-based medical food was well-tolerated, when added to the standard of care, and demonstrated improvements in both overall IBS symptom severity and IBS-D symptoms within just 2 wk.

Key Words: Diarrhea-predominant irritable bowel syndrome; Amino acid beverage formulation; Pragmatic real-world study; Medical food; Bristol Stool Form Scale; Irritable Bowel Syndrome – Severity Scoring System

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Core Tip: Amino-acid based medical foods have been shown to alleviate symptoms of drug induced gastrointestinal side effects, especially diarrhea severity. Diarrhea predominant irritable bowel syndrome (IBS-D) is a chronic gastrointestinal disorder that affects up to 9% of people worldwide. In this pragmatic, real-world study, an amino acid beverage was demonstrated to be tolerable and efficacious when used as an adjunct to standard of care for adults with IBS-D. Participants demonstrated improvements in both overall irritable bowel syndrome symptom severity and IBS-D symptoms within just two weeks. These results suggest that this amino acid-based beverage can be safely integrated into IBS-D standard of care for symptom improvement.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic and debilitating gastrointestinal disorder with a population prevalence of 4%-5% in North America and 4%-9% globally[1,2]. Healthcare professionals employ the Rome IV criteria for diagnosis and treatment decisions. As defined by Rome IV criteria, the predominant diagnosis for IBS is the presence of recurrent abdominal pain or discomfort in conjunction with changes in bowel habits[3]. IBS is further categorized based on the primary stool pattern, with 40% of IBS patients experiencing changes in stool frequency and consistency equating to diarrhea, thus making diarrhea predominant IBS (IBS-D) the most prevalent subtype of the syndrome[4] and one of the most common causes of chronic diarrhea within the United States (est. 5% general population)[5]. International gastrointestinal societies characterize IBS-D for patients who experience > 25% of bowel movements having Bristol[6] stool types of 6 or 7 (watery) and < 25% of Bristol stool types of 1 or 2 (hard)[7]. While the pathophysiology of diarrhea in IBS-D is not precisely understood, the frequent passing of loose or liquid stool can be attributed to some imbalance in the normal function of the small and large intestine responsible for the secretion and absorption of various substrates, ions, and consequently water[5,8].

The management of patients with IBS is tailored to the individual and a holistic approach is recommended that can include dietary, lifestyle, medical and behavioral interventions[9]. While diet modifications such as low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diets are recommended to help alleviate global symptoms[10], strict food avoidance can become unsustainable for some patients and can also compound malabsorption nutrient deficits[11,12]. More specifically, these dietary recommendations do not address water and electrolyte losses that result from diarrhea suffered by IBS-D patients[13,14]. The correction and replacement of these nutrients often go overlooked, with the mainstay of treatment strategy focusing instead on treatments to reduce diarrhea [15].

Providing nutritional support for other conditions where patients suffer from recurrent watery diarrhea has been demonstrated to be a successful approach. For example, an amino acid based medical food is being used by patients undergoing cancer treatments who suffer from prolonged watery diarrhea associated with radiation and chemotherapy. The effects of chemotherapy on the small intestine include nutrient malabsorption, hypersecretion (diarrhea), and increased intestinal permeability[16,17]. Select amino acid formulations have been shown to reduce secretions and improve nutrient absorption in animals[18].

The present study investigated a medical food which contains a select amino acid blend, in combination with ingredients designed specifically to support IBS-D nutritional deficits occurring with diarrhea[11,12]. The objective was to assess the tolerability of the product when added to the standard of care in adults with IBS-D, whilst also measuring any additional benefits conferred to functional gastrointestinal symptoms in a pragmatic real-world setting.

MATERIALS AND METHODS

Study population

The study population consisted of adults between the ages of 18 and 65 years, residing across the United States, who had received a confirmed diagnosis of IBS-D from a qualified physician. Recruitment for this study was conducted through a decentralized approach, leveraging virtual platforms and online resources to reach and engage eligible participants nationwide. To confirm adherence to the Rome IV criteria, participants underwent a 2-week run-in period during which they utilized an electronic diary each day to record their predominant stool type on the Bristol Stool Form Scale (BSFS)[6] and the severity of abdominal pain/discomfort using numeric rating scales graded on an 11-point scale. Eligibility for the study was determined by specific criteria: participants had to experience diarrhea, defined as stool types 6 and 7 on the BSFS, occurring at least four times weekly and constituting the predominant (> 25%) stool pattern. Additionally, they were required to report abdominal pain and/or discomfort occurring at least once a week and possess a Functional Bowel Disorder Severity Index (FBDSI) score exceeding 60[19]. Throughout their participation in the trial, eligible participants were allowed to maintain their current therapeutic regimens, supplements, and dietary practices.

Exclusion criteria encompassed a diagnosis of IBS-C or unclassified IBS according to the Rome IV criteria, as well as diagnoses of other gastrointestinal disorders such as Crohn's disease, colitis, and celiac disease. Women who were pregnant or breastfeeding were ineligible for participation. Additionally, patients with known allergies to the components of the test product or those anticipating modifications to their regular medications that might impact bowel habits were excluded from the study.

Study design

The clinical study was conducted in a fully decentralized manner within the United States, adhering to the principles outlined in the International Council on Harmonization E6 Good Clinical Practice, and in compliance with local regulatory requirements. The study was approved and monitored by an independent institutional review board (Advarra Institutional Review Board, Columbia, MD).

This is a pragmatic real-world study, conducted in an open-label, single-arm design, comparing a 2-week baseline assessment to a subsequent 2-week intervention period. The study was administered through the Laina Clinical Research Platform. The study population was recruited *via* virtual channels, including online advertisements, and in partnership with the Walmart Health Research Institute, which facilitated the validation of participants' health records and physician diagnoses after obtaining informed consent. Eligible participants underwent a 2-week run-in period to assess baseline parameters, thereby informing their inclusion in the study. Data were collected electronically through a mobile phone application with participants engaged in completing daily electronic diaries.

Participants enrolled into the intervention trial period received sixteen 16-ounce bottles of enterade® IBS-D and were instructed to drink 8-ounces once in the morning (30 min prior to eating) and 8-ounces once in the evening (30 min prior to eating) for 14 d. Each day during the intervention period, participants filled out daily symptom diaries with outcome measures described below. Additionally, validated surveys from the Rome Foundation were used to monitor patient reported IBS-D associated symptoms, including the IBS-Severity Scoring System (IBS-SSS)[20] and the Global Improvement Survey (GIS)[21]. Participants filled out the IBS-SSS on days 0 and 14, and the GIS on day 14 as a final questionnaire about the overall study experience. Day 0 was the last day (day 14) of the run-in period, whereas day 14 was the last day of the intervention period.

Study product

The amino acid based medical food beverage used in this study was enterade® IBS-D, which contains a patented blend of plant-based amino acids (valine, aspartic acid, serine, threonine, tyrosine), electrolytes (sodium, potassium, chloride), vitamins (ascorbic acid), and minerals (zinc, copper, calcium) carefully selected to help replenish the loss of water, electrolytes and other nutrients that occur secondary to frequent diarrhea and help to support and maintain normal digestive function in IBS-D. The liquid product (mixed berry lot IBSD-0001; orange lot IBSD-0002) is specially manufactured and processed in compliance with medical food regulations in the United States and designed to be consumed on a partial basis in patients exclusively with the specific medical condition of IBS-D. It is for the partial oral feeding and hydration of an individual with IBS-D and is formulated based upon research demonstrating the unique nutritional needs and requirements of those with the disease, including hydration, select vitamins, minerals and electrolytes which differ from the nutritional needs of healthy normal individuals. The proper use of the product as part of the management of the disease incorporated in the medical nutrition therapy, is by the guidance of the health care practitioner.

Outcome measures

The primary outcome, measure of tolerability, was assessed by the number of Adverse Events (AEs) spontaneously reported by participants for the duration of the study. Any event occurring after obtaining participant consent was recorded as an AE, which was defined as any unfavorable and unintended diagnosis, symptom, sign, syndrome, or disease which either occurred during the study, having been absent at baseline, or if present at baseline, appeared to worsen. All AEs were recorded according to the common terminology criteria for AEs (CTCAE Version 6.0), regardless of their relationship to the study intervention.

The Food and Drug Administration emphasizes the difference between statistical significance and clinical relevance in their IBS guidance for industry[22]. While our product is a medical food, where relevant we examined potential product benefits for secondary outcomes considering clinically based rules, including 'responder' analyses[22] and minimally clinically important differences (MCID)[23]. Stool consistency was assessed *via* the BSFS, a validated ordinal scale of stool types ranging from 1 through 7, with types 6-7 being indicative of diarrhea. BSFS responders were defined as those with a 50% decrease in the number of days per week with at least one type 6-7 bowel movement relative to baseline which meets the level of a "responder". Baseline is defined here as the 2-week run-in period. The number of days were included for the baseline across both weeks of the run-in, and a similar approach was taken for week 2 of the trial period.

Abdominal pain and discomfort severity was assessed *via* an 11-point numeric rating scale (APS-NRS)[23], with 10 representing most severe pain and 0 representing no pain. Pain responders and discomfort responders were defined as those participants recording a 30% decrease in, respectively, the mean weekly pain and discomfort score on the NRS. The average pain/discomfort was calculated across the 2-week run-in period and compared to the average pain/discomfort scores in week 2 of the trial period.

Urgency or severity of urgency was recorded on a 4-point Likert scale from 0 (None) to 4 (Severe urgency). Improvement and/or worsening on the urgency scale was defined as the difference between the maximum urgency score at baseline (2-week run-up) and during the trial period. Category changes were derived (maximum urgency trial period minus maximum urgency at baseline) and designated as follows: "Significant improvement/worsening", a 3-category change; "moderate improvement/worsening", 2-category change; "improvement /worsening", and 0, "No change".

The change in IBS symptom severity, assessed *via* the IBS-SSS total score[20] was assessed from baseline to day 14. Scores on the IBS-SSS range from 0 to 500, with five domains related to abdominal pain severity and frequency, abdominal distention, dissatisfaction with bowel habits, and interference with quality of life. A decrease of 95 points has been associated with a clinically meaningful improvement[23] and was used for classification of IBS-SSS responders.

Statistical analyses

Study data are summarized using means (SD). The denominator to determine the percentage of participants in each category is based on the number of participants with complete paired data unless otherwise noted. A descriptive analysis was used for the primary, secondary, and exploratory outcomes. The IBS-SSS efficacy analysis evaluated the changes (day 0 *vs* day 14) using a paired *t*-test. All statistical analyses were performed using R package 1.3-0 or GraphPad Prism v 9.4.0.

RESULTS

A total of 987 screened patients who participated in the 2-week run were assessed for eligibility and 100 participants were enrolled into the study intervention period (Figure 1). Enrollment and intervention occurred continuously from October 2022 through May 2023. All 100 participants who participated in the 2-week intervention period completed the study.

Baseline characteristics are presented in Table 1. The mean age of participants were 39.7 (SD 10.6), with 67% being female. All patients met the ROME IV criteria for IBS-D and had baseline mean IBS-SSS and FBDSI scores of 314 (77) and 195 (52.6) respectively. The average BSFS and APS-NRS scores were 6 (0.1) and 6 (0.2) respectively. The average IBS-SSS, BSFS and APS-NRS scores indicate moderate to severe IBS-D symptomology at study outset. A summary of the standard of care therapies is provided in Table 2.

Tolerance to the amino acid-based medical food, taken twice daily for a period of 14 d, was excellent. Every participant successfully completed the full 14-day trial, and there were no instances of dropouts or discontinuation of the study product reported. Only two Treatment Emergent AEs were spontaneously reported over the course of the study. Both events were reported by the same participant, who experienced a bout of abdominal bloating followed by a temporary increase in abdominal discomfort. The AEs were characterized as mild, and they were self-limiting, with no need for discontinuation of the test product. Importantly, neither of these events was deemed to be a serious adverse event.

Table 3 shows the responder analysis for the secondary outcomes of the study. The number of IBS-D stool consistency responders, based on a decrease of 50% or more in the number of days per week with at least on type 6-7 bowel movement, as compared to baseline was 40 (40%). The number of IBS-D pain and discomfort responders who exceeded a clinically meaningful threshold with a reduction of 30% mean weekly pain and discomfort were 51 (53%) and 53 (55%) respectively. The number of participants who achieved both clinically meaningful responses in pain/stool consistency or discomfort/stool consistency were 24 (25%) for both composite endpoints. Table 4 presents the overall improvement in the amount of urgency experienced by participants, with 58% of participants achieving some level of improvement.

Seventy-one participants provided complete IBS-SSS data on days 0 and 14 for pairwise comparison. Figure 2 illustrates the differences in each of the 5-item IBS-SSS endpoints and their significant improvement over 14 d. Individual and significant average changes in the aggregate IBS-SSS experienced by participants are shown in Figure 2. Three participants began the study with mild scores (75 to 175; 4%), n = 29 began with moderate scores (176 to 300; 41%), and n = 39 began with severe scores (301 to 500; 55%). Overall, 75% (53/71) of participants experienced a reliable clinical score

Table 1 Baseline socio-demographic details

Characteristic	*n* = 100[1]
Sex	
Female	67 (67%)
Male	33 (33%)
Age (mean, SD)	39.7 (10.6)
Ethnicity	
American Indian/Alaska Native	8 (8%)
Asian	2 (2%)
Black	9 (9%)
Native Hawaiian or other Pacific islander	1 (1%)
White	80 (80%)
Hispanic	
Hispanic/Latino	10 (10%)
Non-Hispanic	90 (90%)
IBS-D features	
Met Rome IV Criteria	100 (100%)
Number of patients with > 4 d experiencing type 4/5 stools	100 (100%)
Average BSFS	6 (0.1)
Average pain-NRS	6 (0.2)
IBS-SSS[2]	314 (77)
FBDSI	195 (52.6)

[1]*n* (%) or mean (SD).
[2]*n* = 71 (only 71 pairs of the irritable bowel syndrome severity scoring system were completed by participants).
IBS-SSS: Irritable bowel syndrome severity scoring system; BSFS: Bristol Stool Form Scale; NRS: Numeric rating scale; FBDSI: Functional Bowel Disorder Severity Index; IBS-D: Diarrhea predominant irritable bowel syndrome.

Table 2 Overview of standard of care practices

Dietary modifications	*n* = 100[1]	Concomitant supplements	*n* = 100[1]	Concomitant medication	*n* = 100[1]
FODMAP	50 (50%)	Prebiotics	60 (60%)	Rifaximin	35 (35%)
Gluten-free	51 (51%)	Probiotics	76 (76%)	Eluxadoline	22 (22%)
Keto	36 (36%)	Peppermint oil	45 (45%)	Antispasmodics	12 (12%)
Elimination	50 (50%)	Fiber	86 (86%)	SSRIs	8 (8%)
High fiber	53 (53%)	Ginger	52 (52%)	Tricyclic antidepressant	8 (8%)
Low fiber	43 (43%)	Magnesium	55 (55%)	Anticholinergic medication	14 (14%)
-	-	Vitamin D	57 (57%)	Antidiarrheal medications	32 (32%)
-	-	-	-	Bile acid sequestrants	9 (9%)
-	-	-	-	Ondansetron	8 (8%)

[1]*n* (%).
FODMAP: Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; SSRIs: Selective serotonin reuptake inhibitors.

Table 3 Diarrhea predominant irritable bowel syndrome responder analysis

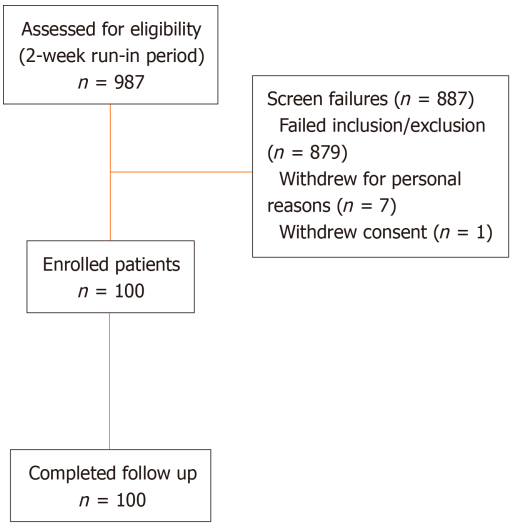
Characteristic	*n* (%)
BSFS responder (*n* = 100)	40 (40%)
Pain responder (*n* = 96)	51 (53%)
Discomfort responder (*n* = 96)	53 (55%)
Composite responder (pain) (*n* = 96)	24 (25%)
Composite responder (discomfort) (*n* = 96)	24 (25%)
IBS-SSS (*n* = 71)	36 (51%)

IBS-SSS: Irritable bowel syndrome severity scoring system; BSFS: Bristol Stool Form Scale.

Table 4 Overview of maximum weekly urgency experienced between baseline and intervention period

Urgency	*n* = 98[1]
Category change	
Significant improvement	8 (8%)
Moderate improvement	9 (9%)
Mild improvement	40 (41%)
No change	40 (41%)
Mild worsening	1 (1%)

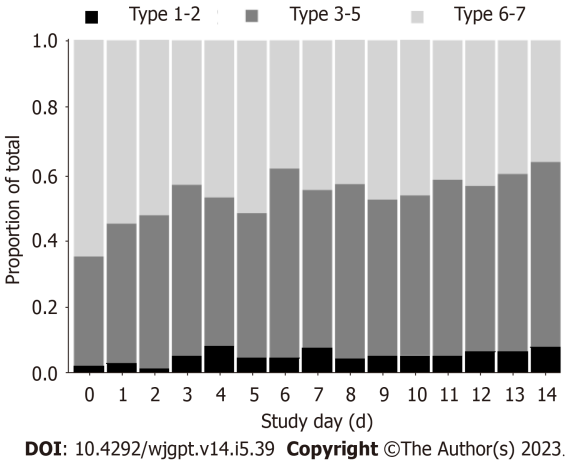
[1]*n* (%).



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Figure 1 Participant flow chart.

improvement (Figure 2). In addition, 51% of participants experienced ≥ 95-point score improvement, often considered the MCID[23]. The mean score reduction (-109.4, 95% confidence interval: -130.1, -88.8) exceeded both thresholds[20,23]. A category shift from severe to moderate or mild occurred in 69% of participants (27/39) and a shift from moderate to mild categories occurred in 52% of participants (15/29), such that 62% (42/68) of the total moderate to severe IBS-SSS sufferers experienced a full IBS-SSS category improvement. Seventy-six percent of participants (54/71) reported relief on the GIS after 14 d of amino acid beverage consumption.



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Figure 2 Change in proportion of grouped Bristol Stool Form Scale types during 14 d of amino acid beverage consumption. Sample size varies across days.

DISCUSSION

The purpose of this open-labeled, home-use study was to evaluate the tolerability and functional impact of a select amino acid blended medical food in 100 confirmed IBS-D participants using validated survey instruments from the Rome Foundation. The study design was employed to evaluate the effectiveness of an amino acid-based medical food in a pragmatic setting. This approach employed a decentralized methodology to enroll a diverse range of participants while minimizing disruptions to routine care, thereby ensuring that the study findings are relevant to real-world clinical practice. Strict enrollment criteria ensured that participants had recurring watery diarrhea. Further, the 2-weeks of daily consumption of an amino acid-based medical food demonstrated that the product was safe and tolerable in 100% of the population tested and had a significant positive impact on the exploratory variables assessed.

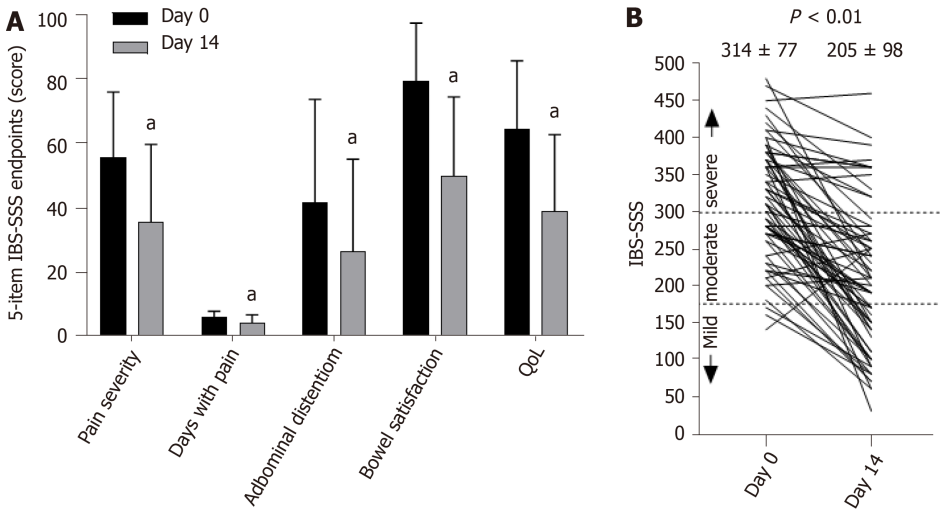
The daily consumption of approximately 474 mL (16 fl. oz.) of an amino acid-based medical food beverage for 2-weeks drastically reduced the group percentage of BSFS 6-7 from 65% to 36% (Figure 2). Chronic diarrhea in IBS-D may double or triple ordinary stool frequency[3]. In conjunction with stool quality of BSFS 6-7[7], IBS-D may increase daily bowel water losses to 500 mL[6,24] along with accompanying salt losses[8,25]. Although no measures of hydration status were made in this study, the complement of approximately 474 mL of fluid with approximately 30 mmol/L of key electrolytes consumed daily, alongside a significant reduction in BSFS from liquid to solid, makes plausible an improvement in whole body hydration status over the 2-weeks. The improvements in BSFS over the 14-day product intervention period are entirely consistent with the reduced stool frequency benefits reported in previous studies consuming amino acid-based beverages with ancillary compositional differences to the product tested herein[26-29]. Hypotonic oral rehydration therapy is widely recognized as the preferred intervention for diarrhea and dehydration independent of etiology[13,30,31]. However, a dual action product that rehydrates while reducing gastrointestinal symptoms (*e.g.* diarrhea), as reported in this study, has not been previously demonstrated[32].

The IBS-SSS is a widely used consensus-based measurement of IBS-D severity[20]. Consumption of an amino acid beverage for 2-weeks resulted in improvements on all 5-IBS-SSS survey items (Figure 3A). The mean overall improvement on the IBS-SSS was 109 points (Figure 3B). Seventy-five percent of participants improved by a clinically meaningful score of at least 50 points[20], improvements similar for IBS-D patients on a starch and sucrose restricted diet for 4-weeks (82.3%)[33]. The overall improvement reported on the GIS in this study (76%) was comparable to the 80% improvement reported in the initial 2-weeks of a pharmaceutical IBS-D intervention trial of Solifenacin[34].

While an open label study improves ecological validity, there are some inherent limitations to this study design. First, evaluations were based exclusively on patient reported outcomes and the possible involvement of the placebo effect in the results cannot be excluded. Since pooled estimates of placebo response are estimated[35-37] to range from 22% for composite pain and stool assessments, 39.6% for pain and discomfort, 33% stool consistency, and 43% for IBS-SSS it is acknowledged that placebo response rate is quite high and inconsistent across studies. Even when taking this into consideration, the present study verified that an amino acid based medical food can confer additional health benefits when used as an adjunct to the standard of care (Table 3) in line with clinically meaningful improvements beyond common placebo effects recorded in the above cited literature.

Second, the short duration of this pilot trial can be viewed as both a limitation and a benefit. The limitation resides in the fact that IBS-D is a lifelong, chronic condition so the durability of benefit observed after 2 weeks remains unknown. The benefit is the observed significance and magnitude of effects on par with other dietary interventions used for much longer time periods. Of note, low FODMAP diets are recommended by consensus for IBS[10] and often produce excellent outcomes (*e.g.*, Russo *et al*[38]). But unlike a daily amino acid beverage, low FODMAP diets can become impractical, tiresome, and even unhealthy as a long-term solution for IBS-D.

Finally, the study was structured intentionally to provide real-world patient experiences (open-label, standard of care) within a controlled clinical trial framework. This approach yields valuable insights into the practical use, benefits, and risks of using a medical food as an adjunct (rather than a replacement) to existing care, demonstrating its effectiveness in



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Figure 3 Change in irritable bowel syndrome severity scoring system survey items and overall improvement on the irritable bowel syndrome severity scoring system. A: Change in individual 5-item irritable bowel syndrome severity scoring system (IBS-SSS) scores following 14-days of amino acid beverage consumption (n = 71 pairs). Lower scores indicate improvement. [a]P < 0.05; B: Change in global IBS-SSS following 14 d of amino acid beverage consumption. The mean difference was significant by paired t-test (n = 71 pairs).

broader healthcare settings. However, while the use of patient reported outcomes in IBS research is essential[39], future studies that include direct blood and fecal markers will complement and add strength to the conclusions drawn from pragmatic studies like this one.

Importantly, this study addresses the replenishment of water and nutrients lost due to diarrhea in IBS-D patients, which is a nutritional complement to the gut benefits afforded by the amino acids. Until now, there has not been a specifically formulated medical food available to address the nutritional deficits experienced by IBS-D patients[11,12,24]. As previously mentioned, the most recent guidelines for managing patients with IBS emphasize the importance of tailoring treatments to individual needs and adopting a holistic approach that encompasses dietary, lifestyle, medication, and behavioral interventions[10]. The open label study design in the present study exemplifies this approach, as participants were employing all the previously mentioned modalities and practices. It is also important to note that despite the use of these modalities and practices (Table 2), participants in the study did exhibit recurring watery diarrhea to the degree that met inclusion criteria for participation in the study. However, the positive improvements in gastrointestinal symptoms reported in the present study demonstrate that this specifically formulated medical food can be used in conjunction with other approaches.

CONCLUSION

Patient reported outcomes collected in this pragmatic study provide evidence that the integration of an amino acid-based medical food as an adjunct to the standard care for patients with IBS-D is both feasible and well-tolerated. Furthermore, the improvements in gastrointestinal symptoms demonstrated statistically significant benefits with an order of magnitude on par with longer nutrition intervention trials (*e.g.*, Gayoso *et al*[33]; Russo *et al*[38]). Lastly, a specifically formulated amino acid beverage appears a promising adjunct approach for individuals suffering from IBS-D in relieving gastrointestinal symptoms.

ARTICLE HIGHLIGHTS

Research background

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder characterized by recurrent abdominal pain and changes in bowel habits. Diarrhea predominant IBS (IBS-D) is the most prevalent subtype, causing chronic and debilitating diarrhea. This study explores the potential benefits of an amino acid based medical food, enterade® IBS-D, to address nutritional deficits in IBS-D patients and improve their gastrointestinal symptoms, aiming to provide an additional means to management.

Research motivation

The motivation to perform this research was to discover additional therapies to aid in the management of chronic diarrhea and associated symptomology resulting from IBS-D.

Research objectives

The study primarily focused on the tolerability of the amino acid based medical food by monitoring adverse events (AEs) reported by participants. Secondary outcomes were assessed using a number of clinical criteria, including changes in stool consistency [Bristol Stool Form Scale (BSFS)], reduction in abdominal pain and discomfort, improvement in bowel urgency, and changes in the overall IBS-Severity Scoring System. The study considered both statistical significance and clinical relevance as recommended by the Food and Drug Administration for IBS-related assessments.

Research methods

The study used a decentralized, open-label, single-arm design, with data collected electronically through the Laina Clinical Research Platform during a 2-week baseline assessment and a subsequent 2-week intervention period, where participants consumed enterade® IBS-D. The study included adults aged 18-65, diagnosed with IBS-D in the United States. Participants were evaluated during a 2-week run-in period to confirm their diagnosis using Rome IV criteria. Eligible participants needed to experience diarrhea at least four times weekly (BSFS types 6 and 7), along with abdominal pain/discomfort and a Functional Bowel Disorder Severity Index score above 60. Exclusion criteria included other IBS subtypes, gastrointestinal disorders, pregnancy/breastfeeding, allergies to the test product components, and anticipated medication changes that could affect bowel habits. Outcome measures included daily symptom diaries, the IBS-Severity Scoring System, and the Global Improvement Survey (GIS) from the Rome Foundation.

Research results

The study involved 100 participants with IBS-D who completed a 2-week intervention period. All participants met ROME IV criteria for IBS-D, and their baseline IBS severity scoring system (IBS-SSS) score and FBDSI scores indicated moderate to severe symptomology. Tolerance to the amino acid-based medical food was exceptional, with no dropouts or discontinuations, and only two mild AEs reported. Responder analysis for secondary outcomes revealed that 40% of participants achieved a 50% or more decrease in days with type 6-7 bowel movements. Additionally, 53% and 55% experienced clinically meaningful reductions in pain and discomfort, respectively. About 25% of participants achieved meaningful responses in both pain/stool consistency or discomfort/stool consistency. Fifty-eight percent of participants showed improvements in urgency. IBS-SSS data demonstrated significant improvement, with 75% experiencing a reliable clinical score improvement, 51% achieving a ≥ 95-point score improvement, and a category shift from severe to moderate or mild in 69% of participants. Furthermore, 76% reported relief on the GIS after 14 d of amino acid beverage consumption.

Research conclusions

The study suggests that adding an amino acid-based medical food to the standard care for IBS-D patients is practical and well-tolerated. The improvements in gastrointestinal symptoms were statistically significant and comparable to longer nutrition intervention trials, making this amino acid beverage a promising adjunct for relieving IBS-D symptoms.

Research perspectives

While patient reported outcomes in IBS research are crucial endpoints, future studies that include collection of biological samples, such as direct blood and fecal markers, will supplement and strengthen the conclusions that have been drawn from this pragmatic study.

FOOTNOTES

Author contributions: Niles SE, Cheuvront SN, Kenefick RW, and Fawkes N designed the research study; Niles SE, Blazy P, Cheuvront SN, Kenefick RW, Vidyasagar S, Smith AB, Fawkes N, and Denman W analyzed the data and wrote the manuscript; Denman W acted as the Principal Investigator; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Advarra Institutional Review Board (Approval No. Pro00065894).

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All authors are employees of Entrinsic Bioscience LLC (EBS) and EBS was the research sponsor. Patent 174821-011205/PCT (PCT/US11/53265) is issued to EBS Holdings, and patent 174821-012001/PCT (PCT/US13/25294) is issued to EBS Holding.

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