



Applied nutritional investigation

Palmitoylethanolamide and polydatin in pediatric irritable bowel syndrome: A multicentric randomized controlled trial



Giovanni Di Nardo M.D., Ph.D.^a, Luca Bernardo M.D.^b, Cesare Cremon M.D.^c, Giovanni Barbara M.D.^c, Enrico Felici M.D.^d, Melania Evangelisti M.D., Ph.D.^a, Alessandro Ferretti M.D.^a, Silvia Furio M.D.^a, Marisa Piccirillo M.D.^a, Flaminia Coluzzi M.D.^{e,f}, Pasquale Parisi M.D., Ph.D.^a, Angela Mauro M.D.^b, Clelia Di Mari M.D.^b, Francesco D'Angelo M.D.^g, Maurizio Mennini M.D., Ph.D.^{a,*}

^a Sapienza University of Rome, NESMOS Department, Pediatric Unit, Sant'Andrea University Hospital, Rome, Italy

^b Pediatric Unit, Department of Childhood and Developmental Medicine, Fatebenefratelli-Sacco Hospital, Milan, Italy

^c Department of Medical and Surgical Sciences, University of Bologna and IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy

^d Pediatric and Pediatric Emergency Unit, "Umberto Bosio" Center for Digestive Diseases, The Children Hospital, AO SS Antonio e Biagio e C. Arrigo, Alessandria, Italy

^e Sapienza University of Rome, Department of Medical and Surgical Sciences and Biotechnologies, Polo Pontino, Latina, Italy

^f Unit of Anaesthesia, Intensive Care and Pain Medicine, Sant'Andrea University Hospital, Rome, Italy

^g Sapienza University of Rome, NESMOS Department, General Surgery Unit, Sant'Andrea University Hospital, Rome, Italy

ARTICLE INFO

Article History:

Received 1 December 2023

Received in revised form 3 February 2024

Accepted 12 February 2024

Keywords:

Irritable bowel syndrome
Palmitoylethanolamide
Abdominal pain
Pediatric patients
Placebo

ABSTRACT

Objective: This study aimed to evaluate the efficacy and safety of co-micronized palmitoylethanolamide (PEA)/polydatin (PD) in the treatment of abdominal pain symptoms in pediatric patients with irritable bowel syndrome (IBS).

Methods: This was a multicenter trial conducted at three Italian pediatric gastroenterology centers, employing a double-blind, placebo-controlled, parallel-arm design. Participants were ages 10 to 17 y and met Rome IV criteria for pediatric IBS. They were randomly allocated to receive either co-micronized PEA/PD or placebo, administered three times daily in a 1:1 ratio, over a 12-wk period. The study assessed baseline severity using the IBS-Severity Scoring System (IBS-SSS) at enrollment and after 4, 8, and 12 wk of treatment. Abdominal pain frequency was assessed on a scale from 1 to 7 d/wk, while stool consistency was classified using the Bristol Stool Scale (BSS) to categorize various IBS subtypes. The primary outcome was the percentage of patients who achieved complete remission, defined as IBS-SSS score <75 points after 12 wk of therapy.

Results: The study involved 70 children with IBS. Of the participants, 34 received co-micronized PEA/PD, and 36 received a placebo. As compared with the placebo group, the co-micronized therapy group had significantly more patients achieving complete remission after 12 wk ($P = 0.015$), with particular benefit in the IBS-diarrhea subtype ($P = 0.01$). The treatment group also experienced a significant reduction in abdominal pain intensity and frequency compared with the placebo group. No adverse events were recorded during the study period.

Conclusions: Co-micronized PEA/PD is a safe and effective treatment to treat abdominal pain symptoms in pediatric IBS.

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Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by the presence of recurrent episodes of abdominal pain related to defecation, along with abnormal bowel habits [1].

GDN reports that drugs were provided by Epitech group, Milan, Italy. GDN and LB contributed equally to the manuscript.

*Corresponding author: Tel.: +39 3397267637; Fax: +3933775089.

E-mail address: maurizio.mennini@gmail.com (M. Mennini).

The global prevalence of IBS in children significantly varies among countries, ranging between 1% and 23% [2–5].

Although considered a benign condition, IBS has a noteworthy deleterious effect on children's quality of life and can lead to significant psychological and emotional burdens for both the children and their families [6]. In its most severe manifestations, IBS is associated with a significant financial burden on health care systems, stemming from heightened resource utilization [7].

Despite research efforts, the pathophysiologic mechanisms responsible for IBS remain inadequately understood.

Current evidence suggests that IBS is a brain–gut axis disorder resulting from complex interactions among genetic, environmental, and host factors [8]. Different triggers (diet, microbiota, bile acids, etc.) in genetically predisposed individuals may contribute to the disruption of the intestinal barrier function, allowing the passage of antigens through the mucosal layer [8]. Consequently, mucosal immune responses, particularly mast cell recruitment and activation, can be induced, triggering alterations in GI sensory-motor function and ultimately leading to IBS symptoms [9].

Palmitoylethanolamide (PEA), a saturated fatty acid amide of palmitic acid, is chemically related to anandamide but exhibits a low affinity for cannabinoid receptors. PEA belongs to the family of ALIAmides, whose name comes from the mechanism of action via autacoid local injury antagonism (ALIA), as it downregulates hyperactivated mast cells and participates in the control of neuro-inflammation and nociception [10]. Furthermore, PEA has been shown to diminish human colonic permeability, both in vitro and in vivo [11]. Interestingly, alongside its activity as a mast cell modulator [12] and a possible agonist for cannabinoid 2-like receptors, PEA may act as an agonist for peroxisome proliferator-activated receptor- α , transient receptor potential vanilloid type 1, and orphanG protein-coupled receptor GPR55 [13]. For these reasons, PEA has emerged as a potential regulator of nociception [10]. Polydatin (PD), a natural precursor and glycosylated form of resveratrol, is a common dietary component derived from grapes that may act synergistically with PEA in reducing mast cell activation and local oxidative stress [14].

A pilot study conducted in adults with IBS revealed a significant effect of PEA/PD in improving abdominal pain, hinting at its potential as a promising natural approach for managing pain in this condition [15]. Similarly, a recent pilot study involving children with migraine reported significant pain relief and reduction in the number of migraine attacks with the use of PEA, without major adverse drug reactions or interactions [16].

Therefore, we devised a multicenter randomized, double-blind, placebo-controlled study to assess the efficacy and safety of co-micronized PEA/PD in treating abdominal pain symptoms in pediatric patients with IBS.

Material and methods

Study design

This is a multicenter randomized, double-blind, placebo-controlled, parallel-arm trial conducted in three Italian referral centers for pediatric gastroenterology (Sapienza University of Rome, Sant'Andrea University Hospital; Fatebenefratelli-Sacco Hospital, Milan; Santi Antonio e Biagio e C. Arrigo Children's Hospital, Alessandria). The study design was defined according to the internationally recognized guidelines for clinical studies and approved by the local Ethical Committee. Written assent from young patients and informed consent from the legal guardian and patients >14 y were obtained. The trial was registered in US Clinical Trials Registry.

Participants

Eligible participants included children referred to the institutions from November 2022 to November 2023 with suggestive symptoms of IBS. The inclusion criteria comprised a confirmed diagnosis of IBS of any subtype (IBS with constipation, diarrhea [IBS-D], mixed bowel habits) in accordance with the Rome IV criteria [17], age from 10 to 17 y, and negative findings for fecal calprotectin and anti-transglutaminase antibodies.

Exclusion criteria included the current use of nonsteroidal anti-inflammatory drugs, corticosteroids, and mast cell stabilizers, the use of topical or systemic antibiotics in the previous month, the continuous use of stimulant laxatives, major abdominal surgery, inflammatory bowel disease (IBD), infectious diarrhea, allergic diseases, and other organic or psychiatric disorders.

Interventions

The study included a 2-wk screening period and a 12-wk placebo-controlled treatment period (Fig. 1). After the screening phase, eligible patients were

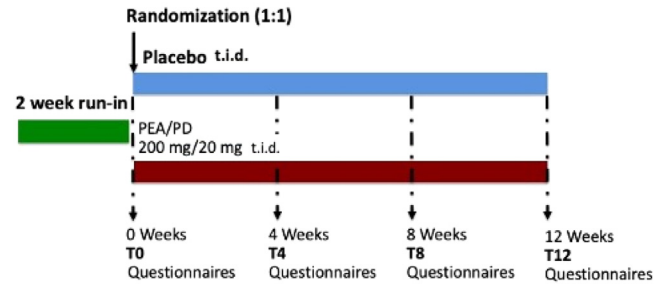


Fig. 1. Study design. PEA/PD, palmitoylethanolamide/polydatin; TID, 3 times a day.

randomly assigned to either co-micronized form (Adolene, Epitech group, Milan, Italy) PEA/PD 200 mg/20 mg, or the equivalent placebo (equal amounts of micro-crystalline cellulose replaced the active principle), three times a day, in a 1:1 ratio, for 12 wk. Study visits were conducted every 4 wk during the treatment period for both groups. All participants were blindly allocated by means of scratch cards to one of the two treatment groups according to a computer-generated randomization list provided by a statistician. An independent statistician used a validated program to generate a randomization list with blocks, block size = 4, preallocated to centers. Patients, caregivers, and study investigators were blinded to the randomization codes. The codes were kept confidential until the end of the study when the randomization code was broken after the database lock. No medications other than the study drug/placebo were allowed during the study.

Efficacy evaluation

The baseline (T0) severity was calculated using the IBS Severity Scoring System (IBS-SSS) at enrollment [18]. Patients were classified as having mild (75–174), moderate (175–299), or severe (300–500) IBS, according to the IBS-SSS severity scale. Abdominal pain frequency was scored from 1 to 7 d/wk.

The Bristol Stool Scale (BSS) was used at each visit to evaluate the consistency of the stools and classify them into various subtypes of IBS. Bristol stool types 1 and 2 are indicative of constipation (BSS C), while types 3 to 5 correspond to normal bowel movements (BSS N), and types 6 and 7 signify diarrhea [19].

The symptom response was assessed after 4 (T4), 8 (T8) and 12 wk (T12) of the trial.

Safety and compliance evaluation

Adverse events (AEs) were recorded through direct interviews during follow-up appointments or via telephone. A collection of empty medication packages verified compliance with treatment at follow-up visits.

Study outcomes

The primary outcome measure was the percentage of patients in each trial arm who achieved complete remission, defined as IBS-SSS score <75 points after 12 wk of therapy. Secondary outcome parameters were a reduction in abdominal pain frequency and changes in bowel habits.

Statistical analysis

The sample size was calculated based on results from a previous study [15] that reported a delta difference of 22.1% in the severity of abdominal pain/discomfort between case-placebo groups, requiring a mean of 29 participants in each group with a power of 90% at the 5% level. From this, to compensate for potential dropouts, it was calculated that 35 patients per treatment arm would have been sufficient to detect this difference with a significance level of α 0.05 (two-sided) and a power of 80%.

We analyzed effectiveness outcomes in the intention-to-treat population (ITT), defined as all participants randomly allocated, regardless of adherence. The normal distribution of data was assessed by means of the Kolmogorov–Smirnov test. Accordingly, the values were expressed as a number and percentage (%) for categorical variables, mean \pm SD for normally distributed continuous variables, or median and interquartile range (25–75 percentile) for non-normally distributed continuous variables. Fisher's exact or χ^2 test was applied for categorical variables. In contrast, the independent *t* test or Mann–Whitney test was used for continuous variables according to the normal distribution of the data. Paired *t* test or Wilcoxon signed-rank test was used for the comparison of the results on the T0 and 2-wk screening period, and a 12-wk placebo-controlled treatment period.

SPSS version 26 (IBM, Armonk, NY, USA) was used for the statistical analysis. $P < 0.05$ was considered statistically significant.

Results

We assessed 96 patients for study eligibility. Of these, 16 were excluded because they did not meet the inclusion criteria, and 10 refused to take part in the study.

Seventy children with IBS were enrolled (mean age 13.7 ± 2.20 y, 32 boys). Thirty-four children were randomly assigned to either co-micronized form PEA/PD 200 mg/20 mg (PEA/PD group), or 36 to the equivalent placebo (placebo group; Fig. 2).

No significant differences were observed between the two groups in terms of demographic characteristics, distribution of IBS subtypes, and baseline measures of IBS severity and IBS-SSS parameters (Table 1).

All enrolled patients took the prescribed PEA/PD and placebo; no patients were lost to follow-up.

In the ITT analysis, the proportion of patients achieving primary end point was significantly higher in the PEA/PD group (17 of 34; 50%) than in the placebo group (8 of 36; 22%; $P = 0.015$, odds ratio, 3.50; 95% confidence interval, 1244–9844; Fig. 3).

Significant distinctions became evident when stratified by IBS subtypes, particularly within the IBS-D subtype (Table 2). In particular, of 26 IBS-D enrolled patients, 7 of 13 (54%) obtained remission after PEA/PD treatment compared with 1 of 13 after placebo (8%; $P = 0.01$).

Additionally, as compared with the placebo group, those in the PEA/PD group exhibited a significant reduction in abdominal pain frequency from T0 to T12 (PEA/PD group T0: 2.89 ± 1.08 versus T12: 1.32 ± 1.22 ; $P < 0.001$; placebo group T0: 2.89 ± 1.10 versus T12: 2.52 ± 1.62 ; $P = 0.1$; Table 3).

Both groups obtained a significant reduction in total IBS-SSS, pain intensity score, and life interference score from T0 to T12 (Table 3). However, upon intergroup comparison, only those in the PEA/PD group exhibited a significant reduction in total IBS-SSS at T12 ($P = 0.01$), pain intensity scores at T8 ($P = 0.04$) and T12 ($P = 0.003$), as well as pain frequency scores at T8 ($P = 0.04$) and T12 ($P = 0.006$), when compared with the outcomes of placebo group (Figs. 4 and 5).

Regarding bowel habit changes, no significant differences were found in children with IBS without diarrhea (i.e., constipation [BSS C, 1 or 2] or normal [BSS N, 3, 4, or 5] bowel habits at enrollment).

Table 1

Baseline characteristics of study participants

	PEA/PD group	Placebo group	<i>P</i> -value
Demographic data			
• Age, y	13.66 ± 2.32	13.77 ± 2.10	0.83
• Sex (M:F)	16:18	16:20	0.63
IBS subtypes			
• IBS-D	13	13	0.83
• IBS-C	8	12	
• IBS-M	13	11	
IBS severity			
• Mild	13	13	0.85
• Moderate	11	13	
• Severe	10	10	
IBS-SSS parameters			
• Total IBS-SSS	253 ± 134.1	239 ± 102.5	0.89
• Pain intensity score	163 ± 89.3	169.4 ± 80.50	0.50
• Life interference score	64.6 ± 36.05	48.44 ± 28.35	0.07
Abdominal pain frequency score	2.89 ± 1.08	2.89 ± 1.10	0.8

IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; IBS-M, mixed variety; IBS-SSS, irritable bowel syndrome severity scoring scale; PEA/PD, palmitoylethanolamide/polydatin. * $P < 0.05$ Student's *t* or Mann-Whitney tests. $P < 0.05$ test.

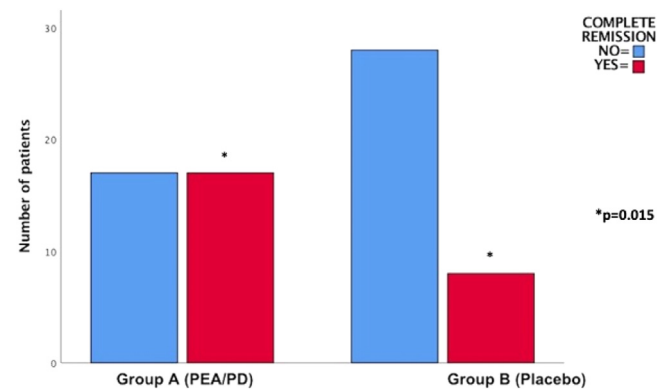


Fig. 3. Differences in the number of patients who achieved complete remission, defined as IBS-SSS < 75 , after 12 wk of therapy in the 2 groups. * $P = 0.015$. IBS-SSS, irritable bowel syndrome severity scoring scale; PEA/PD, palmitoylethanolamide/polydatin.

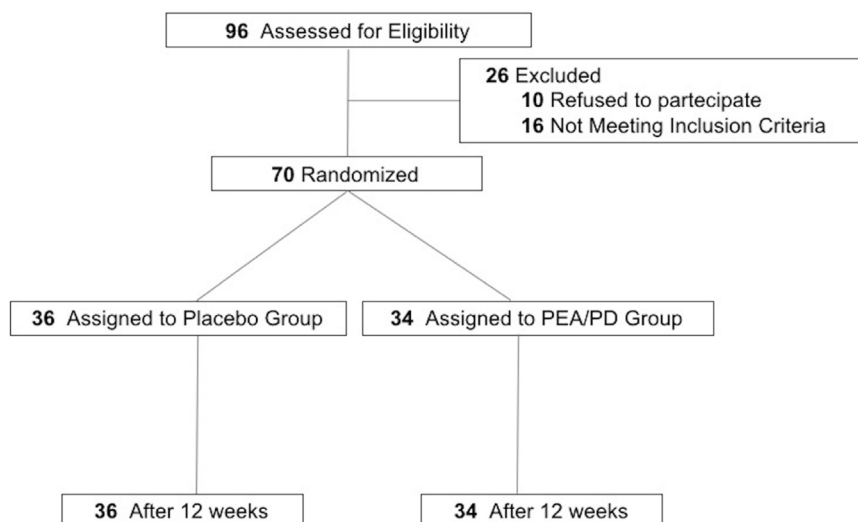


Fig. 2. Consort diagram of the study. PEA/PD, palmitoylethanolamide/polydatin.

Table 2
Differences in remission after treatment in the 2 groups, stratified by IBS subtypes

	PEA/PD group	Placebo group	P-value
IBS-D Complete remission	7/13	1/13	0.01*
IBS-C Complete remission	3/8	3/12	0.55
IBS-M Complete remission	7/13	4/11	0.40

IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; IBS-M, mixed variety; IBS-SSS, irritable bowel syndrome severity scoring scale; PEA/PD, palmitoylethanolamide/polydatin.

* $P < 0.05 \chi^2$ test.

The patients accepted PEA/PD and placebo well, and no AEs were reported in either group. Neither group used rescue medications during the study.

Discussion

The present study showed for the first time that co-micronized PEA/PD is safe and effective in improving abdominal symptoms in children with IBS.

The active treatment notably achieved the primary outcome, with 50% of patients attaining complete remission compared with 22% in the placebo group. Additionally, co-micronized PEA/PD successfully met secondary outcome measures for effectiveness along with various other measures of IBS symptoms.

The fixed association PEA/PD has been successfully used in other forms of chronic visceral pain, such as in pelvic pain syndrome, where the role of neuroinflammation is well recognized [20]. Several investigations highlighted the key role of mast cells in driving peripheral mechanisms of neuroinflammation in different forms of chronic pain [21,22]. Mast cell hyper-activation, which maintains peripheral inflammation and fuels the fire of central sensitization, may be modulated by PEA administration or its analogs [23].

The clinical overlapping of different chronic pain syndromes (i.e., IBD, pelvic pain, endometriosis, fibromyalgia) reflects abdominal and pelvic organ cross-sensitization [24]. Among adolescents, for instance, a significant correlation has been observed between endometriosis and IBD, together with a linear association between pelvic pain severity and the odds of IBD [25]. Neuroinflammation has been identified as the common pathologic pathway, which explains the observed comorbid painful conditions and central microglial activation as the common denominator for both chronic pain and depression, leading to the concept of “sickness behavior” [26].

Therefore, due to a growing body of evidence that supports neuroinflammation and intriguing therapeutic targets for preventing and treating chronic painful conditions, clinical interest for PEA

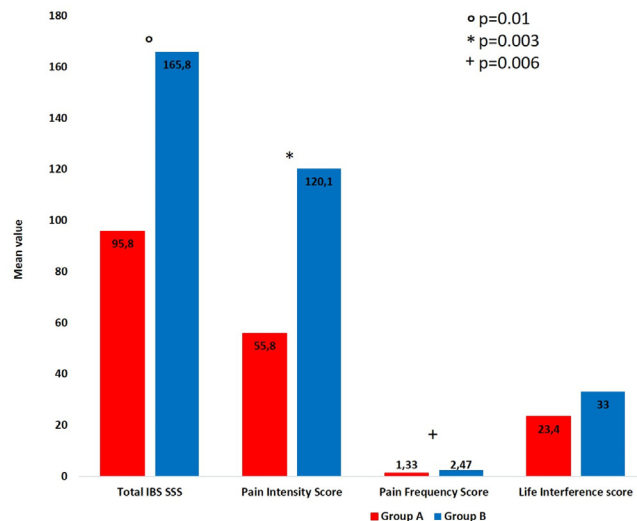


Fig. 4. Differences in total IBS-SSS ($P = 0.01$), pain intensity score ($P = 0.003$), pain frequency score ($P = 0.006$) and life interference score at T12 in the two groups. * $P = 0.01$; † $P = 0.03$; and ‡ $P = 0.006$. IBS-SSS, irritable bowel syndrome severity scoring scale; PEA/PD, palmitoylethanolamide/polydatin.

has been growing. A proof-of-concept study involving adults with IBS showed a significant effect of PEA/PD on improving abdominal pain, indicating a promising role for these nutraceuticals in IBS [15]. The present study represents a pioneering investigation into the same condition in children.

This study boasts several strengths, including a prospective multicenter design, an extended treatment duration of 12 wk, and the application of a well-established objective assessment tool, the IBS-SSS questionnaire. The IBS-SSS is a comprehensive scoring system encompassing all IBS facets, including physical pain, psychological well-being, and overall quality of life. The present study confirmed the reliability and user-friendliness of this score, making it a valuable tool for assessment [1].

High compliance with the study can be found in the tendency of caregivers to search for different therapeutic approaches, often trying to avoid chemicals or synthetic drugs [27].

Nonetheless, there were limitations to the present study. First, we did not have data on the maintenance of remission after discontinuing PEA/PD treatment. Second, the study did not encompass an analysis of the nutritional profile as an outcome variable, thus preventing us from commenting on potential changes in micronutrient profiles.

Table 3
IBS-SSS, life interference score, and symptom response assessed at baseline and after 4, 8, and 12 wk of the trial in the 2 study groups

	PEA/PD group				P-value	Placebo group				P-value
	T0	T4	T8	T12		T0	T4	T8	T12	
Total IBS SSS	253 ± 134.1	213.3 ± 118.8	139.2 ± 72.4	95.8 ± 106.3	0.000*	239 ± 102.5	174.2 ± 94.3	167.5 ± 103	165.8 ± 122	0.000*
Pain intensity score	163 ± 89.3	123.4 ± 69.8	77.5 ± 51.4	55.8 ± 57.1	0.000*	169.4 ± 80.50	130.3 ± 78.5	124.2 ± 88.5	120.1 ± 88.1	0.002*
Life interference score	64.6 ± 36.05	47.6 ± 35.6	34.2 ± 29.7	23.4 ± 34.1	0.000*	48.44 ± 28.35	36.3 ± 21	37 ± 27	33 ± 29.4	0.004*
Abdominal pain frequency score	2.89 ± 1.08	2.53 ± 1.1	1.72 ± 0.9	1.32 ± 1.22	0.000*	2.89 ± 1.10	2.33 ± 1.15	2.40 ± 1.35	2.52 ± 1.62	0.1
Bristol Stool Scale	D = 13 C = 8 N = 13	–	–	1 = 7 2 = 10 3 = 13	0.01† 0.89 0.99	D = 12 C = 11 N = 10	–	–	1 = 7 2 = 11 3 = 12	0.03‡ 0.99 0.89

IBS, irritable bowel syndrome. IBS-SSS, irritable bowel syndrome severity scoring scale; PEA/PD, palmitoylethanolamide/polydatin.

* $P < 0.05$ Wilcoxon signed-rank test.

† $P < 0.05 \chi^2$ test.

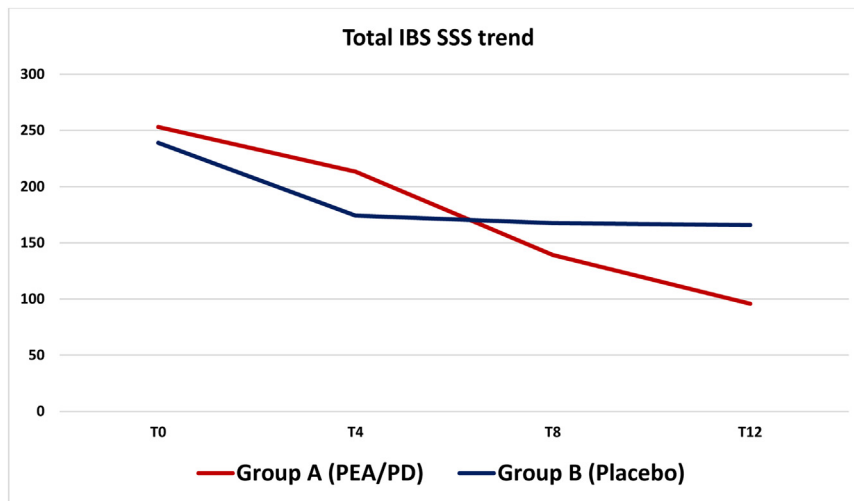


Fig. 5. Total IBS-SSS trend from T0 to T12 in the 2 groups. IBS-SSS, irritable bowel syndrome severity scoring scale; PEA/PD, palmitoylethanolamide/polydatin.

Furthermore, we acknowledge other potential biases: The inclusion criteria might exclude certain subgroups of pediatric IBS patients, and the study relies on self-reported outcomes, such as IBS-SSS, which may be influenced by subjective interpretation.

Despite these limitations, it is important to note that the demographic characteristics, distribution of IBS subtypes, and baseline measures of IBS-SSS parameters were meticulously matched between the two groups, ensuring a fair and robust comparison.

Interestingly, PEA/PD produced a significant difference in IBS-D subtypes (PEA/PD group: complete remission 7 of 13 versus placebo group: 1 of 13; $P = 0.01$), suggesting greater efficacy of the product in this subtype of IBS.

As a secondary outcome, the PEA/PD group exhibited a significant reduction in the frequency of abdominal pain compared with the placebo group, underscoring the therapeutic advantages of the co-micronized treatment. Both groups experienced substantial reductions in total IBS-SSS, pain intensity scores, and life interference scores from baseline to the 12-wk mark. However, in the comparative analysis between the two groups, the PEA/PD group demonstrated superior outcomes. This superiority included a significant reduction in total IBS-SSS at T12, decreased pain intensity scores at T8 and T12, and reduced pain frequency scores at T8 and T12.

These results, therefore, described a significant improvement in the condition during and at the end of therapy with PEA/PD.

The present study confirmed in children the efficacy data shown by Cremon et al. in a population of 54 adult IBS patients versus 12 healthy controls [15]. In that study, however, there was an improvement in the intensity of abdominal pain but not in the frequency of painful episodes. In the present study, however, there is also a significant difference in frequency. It is possible to speculate that this difference is caused by differences that distinguish a pediatric population from an adult one. For example, it has been shown that episodes of acute gastroenteritis could predispose more frequently to the appearance of IBS years later if they occurred in childhood compared with adulthood [28]. This evidence was justified by the immunologic immaturity of the digestive system of pediatric patients and by the notable compositional differences of the microbiota compared with adults. In this same context of vulnerability, however, we should consider substantial differences regarding the distribution of ileocolonic mucosal mast cells and mast cells near nerve fibers in children compared with adults [29].

Hence, there is room for speculation regarding the differential progression of neuroinflammation processes between the two populations. In children, where the temporal development of neuroinflammation phenomena is less established compared with adult patients with a prolonged history of IBS, a potential treatment window may exist. This suggests the possibility of achieving more satisfactory and enduring treatment effects.

Conclusion

Findings from the present study suggested that co-micronized PEA/PD therapy is a safe and effective treatment option for children with IBS. The results underscored its efficacy in symptom improvement and its potential to significantly enhance the overall well-being of pediatric patients with IBS.

In this context, considering the lack of specific treatments for IBS, the use of a nutraceutical product such as PEA/PD appears even more advisable, particularly when administered in a timely manner.

Future research and clinical trials are necessary to confirm and expand on these findings, aiming to establish a valuable and accessible therapeutic approach for this patient population.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Giovanni Di Nardo reports equipment, drugs, or supplies was provided by Epitech group, Milan, Italy. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Giovanni Di Nardo: Writing – review & editing, Supervision, Project administration, Conceptualization. **Luca Bernardo:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Cesare Cremon:** Writing – review & editing, Supervision. **Giovanni Barbara:** Writing – review & editing, Supervision. **Enrico Felici:** Investigation. **Melania Evangelisti:** Writing –

original draft, Software, Data curation. **Alessandro Ferretti**: Validation, Investigation. **Silvia Furio**: Validation, Investigation. **Marisa Piccirillo**: Investigation. **Flaminia Coluzzi**: Validation, Supervision. **Pasquale Parisi**: Validation, Supervision. **Angela Mauro**: Validation. **Clelia Di Mari**: Validation. **Francesco D'Angelo**: Validation, Supervision. **Maurizio Mennini**: Writing – original draft, Supervision, Formal analysis.

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