The therapeutic potential of short-chain fatty acids enemas in inflammatory bowel diseases: a systematic review*

Nina Kaczmarek[1], Marta Kokot[1], Aleksandra Makarewicz[1], Aleksandra Glapa-Nowak[1], Jan K. Nowak[1], Małgorzata Jamka[1], Jarosław Walkowiak[1]

[1] Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences, Poznan, Poland

Farmacja Polska, ISSN 0014-8261 (print); ISSN 2544-8552 (on-line)

Correspondence
Jarosław Walkowiak, MD, PhD;
Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences, Szpitalna Str. 27/33, 60-572 Poznań, Poland, e-mail: jarwalk@ump.edu.pl

Sources of funding
No funding sources indicated

Conflict of interest
J.K.N. reports personal fees from Norsa Pharma and non-financial support from Nutricia, outside the submitted work. J.W. received personal fees and non-financial support from Biocodex, BGP Products, Chiesi, Hipp, Humana, Mead Johnson Nutrition, Merck Sharp & Dohme, Nestle, Norsa Pharma, Nutricia, Roche, Sequoia Pharmaceuticals, and Vitis Pharma, as well as research grants, personal fees and non-financial support from Nutricia Research Foundation Poland, outside the submitted work. Other authors declare that they have no competing interests.

Received: 2020.06.15
Accepted: 2020.07.09
Published on-line: 2020.07.21

DOI
10.32383/farmpol/125114

ORCID
Nina Kaczmarek (ORCID id: 0000-0002-7766-9314)
Marta Kokot (ORCID id: 0000-0003-2862-1127)
Aleksandra Makarewicz (ORCID id: 0000-0001-9310-9643)
Aleksandra Glapa-Nowak (ORCID id: 0000-0002-3017-0524)
Jan K. Nowak (ORCID id: 0000-0003-0953-2188)
Małgorzata Jamka (ORCID id: 0000-0002-0257-6180)
Jarosław Walkowiak (ORCID id: 0000-0001-5813-5707)

The therapeutic potential of short-chain fatty acids enemas in inflammatory bowel diseases: a systematic review

It has been suggested that short-chain fatty acid (SCFA) enemas might improve clinical, endoscopic and histological scores in patients with inflammatory bowel disease. However, despite the promising results of *in vitro* studies, the findings of animal studies and randomized controlled trials are inconclusive. Therefore, this review aimed to assess the efficacy of SCFA enemas in patients with inflammatory bowel diseases. Electronic searches were performed in PubMed, Scopus, Web of Science, and Cochrane databases. Original studies were included in this systematic review if they met the following inclusion criteria: 1) types of studies: parallel or crossover randomized controlled trials; 2) language: articles published in English; 3) types of interventions: SCFA enemas; 4) population: studies conducted in subjects with ulcerative colitis or Crohn's disease of either gender and any age and without restrictions based on the ethnicity of study participants, location of study or sample size. The outcomes included the effect of SCFA enemas on disease activity index (DAI), endoscopic and histological scores. In total, four studies enrolling 187 patients with inflammatory bowel diseases were included in this systematic review. Two studies assessed

* Potencjał terapeutyczny krótkołańcuchowych kwasów tłuszczowych podawanych doodbytniczo w nieswoistych chorobach zapalenia jelit: przegląd systematyczny

the effect of SCFA enemas on DAI. Four studies evaluated the effect of SCFA therapy on the endoscopic score and the histological score. There were no significant differences between the SCFA groups and the control groups regarding the impact on any analyzed parameter. Two studies demonstrated a statistically significant decrease in DAI after the intervention period, both in the SCFA groups and the control groups. Similarly, statistically significant differences between pre- and post-intervention endoscopic scores in the SCFA groups were reported in four studies. However, in three studies, a similar effect was demonstrated in the control groups. Besides, in three studies no effect of SCFA enemas on the histological score was observed. In conclusion, there is no evidence for the effectiveness of SCFA enemas in patients with inflammatory bowel diseases.

Keywords: inflammatory bowel diseases, ulcerative colitis, Crohn's disease; short-chain fatty acid, enema.

© Farm Pol, 2020, 76 (5): 297–304

Introduction

Inflammatory bowel diseases (IBDs) are one of the most significant challenges in modern medicine. It is estimated that seven million people worldwide suffer from ulcerative colitis (UC) and Crohn's disease (CD). These debilitating conditions affect up to 0.5% of the highly industrialized nations and an increasing number of citizens in developing countries, often developing before the 40th year of life, therefore, adversely affect much of a patient's adulthood [1, 2].

Researchers are seeking to identify the cause of IBD, focussing on the genetic and environmental factors as well as the immune system disturbance [3–5]. However, currently, the pathogenesis of these diseases is incompletely understood. The relapsing-remitting nature of IBD and the symptoms, such as diarrhea, constipation, rectal bleeding, abdominal cramps and pain, affect not only the patient's quality of life but also that of the whole family. Medical treatment includes 5-aminosalicylates (5-ASA), corticosteroids, immunomodulators, antibiotics, and biologic therapies, to which not every patient responds [6]. Despite the effectiveness of 5-ASA or corticosteroids, patients are exposed to numerous side-effects. Systemic steroid therapy may lead to metabolic and electrolyte disturbance, weight gain, and also damage to the gastric mucosa [7–9]. In addition, a recent study has demonstrated that clinical remission occurred in 31.3% and 22.5% of UC patients in vedolizumab or adalimumab therapy, respectively [10]. Moreover, up to 44% of patients in ustekinumab therapy successfully maintain remission after 44-week of maintenance therapy [11]. These results are not satisfactory; therefore, researchers have been considering several alternative supplementary therapeutic methods, including the use of short-chain fatty acids (SCFAs).

SCFAs (e.g., acetate, butyrate, propionate) are physiologically active by-products of commensal anaerobic bacteria in the intestinal lumen due to the fermentation of oligosaccharide soluble dietary fiber and resistant starch [12]. SCFAs, as essential nutrients of the colon epithelium, play a role in maintaining the intestinal barrier function having anti-inflammatory and immunomodulatory properties [13, 14]. These fatty acids may also promote the growth of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, by lowering colonic pH [15]. Moreover, reduced SCFAs producers (e.g. *Bacteroidetes*, *Firmicutes*) and lower levels of SCFAs in the feces correlate with the increased risk of IBD [16, 17].

Several studies associate the use of SCFAs enemas with improvement in IBD symptoms in humans [18–20] and rats [21]. In addition, an increase in crypt length, mucosal generation and DNA content of the colonocytes were observed [22]. However, other papers did not report significant effects of this treatment on histologic [23, 24] and endoscopic scores [23]. For this reason, this review aimed to assess the efficacy of SCFAs therapy for IBD.

Materials and Methods

Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses check-list [25] and Cochrane guidelines [26]. Four English databases (PubMed, Web of Science, Scopus and Cochrane Library) were searched using the following MeSH terms and keywords: "inflammatory bowel diseases OR colitis, ulcerative OR idiopathic proctocolitis OR colitis gravis OR Crohn's disease OR Crohns disease OR Crohn's enteritis OR enteritis, regional" AND "fatty acids, short chain OR short-chain fatty acids OR volatile fatty acids OR acetates OR acetic acid OR butyrates OR butyric acid OR crotonates OR hydroxybutyrates OR isobutyrates OR caproates OR propionates OR valterates". To identify further relevant studies and potential studies not captured in the electronic database searches, manual searches of the reference lists of the included papers were performed. The research was conducted from journal inception to March 2020. Before starting the review process, the systematic review protocol was registered in the International Prospective Register of Systematic Reviews, registration number: CRD42020175026.

Study selection

Original studies were included if they met the following inclusion criteria:

1) types of studies: parallel or crossover randomized controlled trial (RCT);
2) language: articles published in English;
3) types of interventions: SCFAs enemas (as a mixture of sodium acetate, sodium propionate and sodium butyrate; participants could also receive standard treatment, e.g., 5-ASA);
4) population: studies conducted in subjects with CD or UC of either gender and any age and without restrictions based on the ethnicity of study participants, location of research or sample size.

No time limitations were applied in searching the databases. Case-series, case-control, case-report studies, cohort studies, observational studies, cross-sectional studies, conference reports, editorial letters, studies available only as abstracts and studies with animal models were excluded from this systematic review.

Quality assessment

Each database was searched by two independent researchers in the three main stages of the extraction process (figure 1). First, the reviewers screened article titles, then abstracts, and finally, full texts for eligibility for inclusion in the systematic review. Disagreements were resolved by discussion between the reviewers until a consensus was reached. All reviewers agreed on the final decision of studies to be included. Regarding missing data, primary authors were contacted for more information.

Risk of bias

Two researchers (A.G.-N. and M.J.) independently assessed the risk of bias using the Cochrane Collaboration tool [26], including the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Criteria for low risk, unclear risk, and high risk of bias per the Cochrane Handbook for Systematic Reviews of Interventions [27] were used.

Data extraction

Eligible studies were reviewed, and the following data were collected:

1) first author's name;
2) year of publication;
3) country;
4) study design and method of blinding;

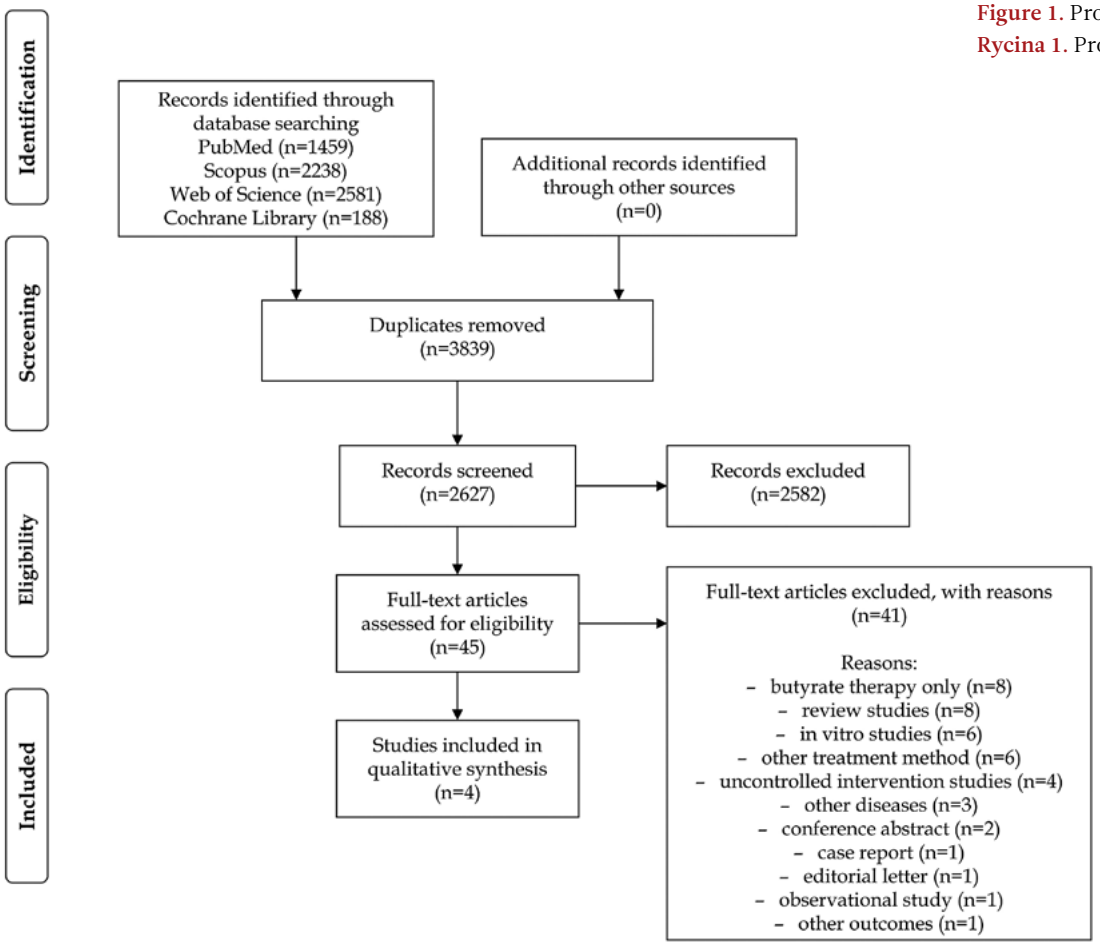

Figure 1. Process of the search.
Rycina 1. Proces wyszukiwania.

5) type of intervention (dose, volume and composition of SCFA, route of administration, length of treatment and type of control);
6) the number of participants and
7) characteristics of study participants (age, sex, origin, and health status).

Outcomes

The outcomes included the effect of SCFAs on disease activity index (DAI), endoscopic and histological scores.

Statistical analysis

Due to the high heterogeneity of the included studies, synthesis in the form of the meta-analysis was not performed, so results from individual studies were dealt with descriptively. A p-value of less than 0.05 was considered statistically significant.

Results

Search results

The electronic database search identified 6,466 potential citations, including 3,839 duplicates, which were removed. The titles and abstracts of the remaining 2,627 records were screened, of which 45 full-text articles were assessed for eligibility. Further assessment excluded 41 articles, as shown in figure 1, with four studies included in the systematic review [20, 24, 28, 29]. No other relevant studies were identified in the other sources searched.

Characteristics of included studies

Table 1 presents the characteristics of the four studies included in the systematic review. All studies were published between 1995 [20] and 2000 [24], three were conducted in Europe (one in Sweden [24], one in Germany [29], one in Italy [20]) and one was from the USA [28]. All studies were classified as RCT [20, 24, 28, 29], of which one had a crossover design [24] and three were parallel [20, 28, 29]. SCFAs (in the form of enemas administered twice a day) were used as an intervention in all studies [20, 24, 28, 29]. In three of them, the enemas contained 80 mM of sodium acetate, 30 mM of sodium propionate and 40 mM of sodium butyrate [20, 24, 28] and in one study, the SCFAs solution included 60 mM of sodium acetate, 30 mM of sodium propionate and 40 mM of sodium butyrate [29]. The control group received enemas with NaCl solution in all studies [20, 24, 28, 29]. In two studies, the pH of administered enemas was 7 [24, 27], one study used 5.5 [29] and one study [20] did not report the pH of the solution used. The volume of enemas was either 60 ml [24, 29] or 100 ml [20, 28], with all patients receiving enemas two times per day [20, 24, 28, 29]. The duration of the intervention varied from 21 [24] to 56 days [29].

Characteristics of the study population

The characteristics of the study populations are shown in table 2. The total sample size was 187 patients: 179 of them had UC [20, 24, 28, 29], eight CD [24]. All studies included both men and

Table 1. Characteristics of included studies.
Tabela 1. Charakterystyka badań włączonych do przeglądu systematycznego.

Study	Year	Country	Type of study	Group	Intervention	Enemas volume [ml/d]	Dose [mM/l]	pH	Duration of intervention [days]
Schauber et al. [24]	2000	Sweden	Double-blind crossover RCT	Intervention	SCFA[2]	120 ml (60 ml × 2)	Sodium acetate 80 mM/l, sodium propionate 30 mM/l, sodium butyrate 40 mM/l	7.0	21[1]
				Control	Saline[2]		N/A		
Breuer et al. [28]	1997	USA	Double-blind parallel RCT	Intervention	SCFA[3]	200 ml (100 ml × 2)	Sodium acetate 80 mM/l, sodium propionate 30 mM/l, sodium butyrate 40 mM/l	7.0	42
				Control	Saline[3]		140 mM/l		
Scheppach et al. [29]	1996	Germany	Double-blind parallel RCT	Intervention	SCFA[3]	120 ml (60 ml × 2)	Sodium acetate 60 mM/l, sodium propionate 30 mM/l, sodium butyrate 40 mM/l	5.5	56
				Intervention	Butyrate[3]		Sodium butyrate 100 mM/l		
				Control	Saline[3]		N/A		
Vernia et al. [20]	1995	Italy	Double-blind parallel RCT	Intervention	SCFA[4]	200 ml (100 ml × 2)	Sodium acetate 80 mM/l, sodium propionate 30 mM/l, sodium butyrate 40 mM/l	N/A	42
				Control	Saline[4]		N/A		

[1] 21 days of intervention and 21 days of placebo; [2] no other drugs were allowed; [3] all patients remained on their respective oral medication, no enemas were allowed; [4] all patients remained on oral mesalazine or sulfasalazine at the usual dosages, no enemas or cortisone were allowed; N/A – not available; RCT – randomized clinical trial; SCFA – short-chain fatty acids;

Table 2. Characteristics of the studied populations.
Tabela 2. Charakterystyka populacji badanej.

Study	Year	Group	n	Age [years]	Sex [% women]	Health status	Montreal classification
Schauber et al. [24]	2000	Intervention	9[1]	43 (23 – 59)[2]	33	Crohn's disease: 8 patients	L3
		Control				Ulcerative colitis: 1 patient	S3
Breuer et al. [28]	1997	Intervention	45[3]	40 ± 12[4]	38	Ulcerative colitis	E2, at least S1
		Control	46[3]	42 ± 14[4]	41		
Scheppach et al. [29]	1996	Intervention[5]	16[1]	40.5[7]	45	Ulcerative colitis	E2, at least S1
		Intervention[6]	15[1]	42.9[7]			
		Control	16[1]	42.9[7]			
Vernia et al. [20]	1995	Intervention	20[8]	41.1 ± 16.7[4]	20	Ulcerative colitis	E2, S1/S2
		Control	20[8]	39.3 ± 13.9[4]	30		

[1] number of patients who were included to the study; [2] median (range); [3] number of patients who completed the study; [4] mean ± standard deviation; [5] treatment with a combination of short chain fatty acids (SCFA); [6] treatment with butyrate enemas; [7] mean; [8] number of patients who were included to the study and completed the study.

women [20, 24, 28, 29], and all patients were adults, mostly middle-aged [20, 24, 28, 29].

Effect of SCFAs administration on DAI

The effect of SCFAs enemas on DAI was assessed in two studies and there were no changes between intervention and control groups (table 3). However, statistically significant differences in DAI between pre- and post-intervention periods were observed both in the intervention groups and the control groups [28, 29].

Effect of SCFAs administration on endoscopic and histological scores

Table 3 presents the effect of SCFAs and placebo on endoscopic and histological scores, which were assessed in all included studies [20, 24, 28, 29]. SCFA was not found to be superior compared to the placebo. Statistically significant differences between pre- and post-intervention periods in the SCFA groups were reported in all studies [20, 24, 28, 29]. However, in three studies, a similar effect was demonstrated in the control groups [24,

Table 3. The effect of SCFA on disease activity index, endoscopic and histological scores.
Tabela 3. Wpływ SCFA na wskaźnik aktywności choroby, wyniki badania endoskopowego i histopatologicznego.

Study	Year	Group	n	Disease activity index		Endoscopic score		Histological score	
				Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Schauber et al. [24]	2000	Intervention	9[1]	N/A	N/A	10 (8 – 10)[2,3]	7 (5 – 10)[2,3]#	5 (0 – 5)[2,4]	4 (4 – 5)[2,4]
		Control					7 (5 – 10)[1,3]#		5 (4 – 6)[2,4]
Breuer et al. [28]	1997	Intervention	45[5]	7.93 ± 1.73[6]	−2.05 ± 0.53[7,8]#	N/A	−0.52 ± 0.16[7–9]#	5.93 ± 2.71[6,10]	−0.37 ± 0.45[7,8,10]
		Control	46[5]	7.51 ± 1.93[6]	−1.19 ± 0.42[7,8]#		−0.37 ± 0.13[7–9]#	5.10 ± 2.72[6,10]	0.69 ± 0.62[7,8,10]
Scheppach et al. [29]	1996	Intervention[11]	16[1]	6.50 ± 1.96[6]	3.60 ± 2.94[6,13]#	6.60 ± 1.99[3,6]	4.10 ± 2.57[3,6,13]#	2.90 ± 2.28[6,5]	3.10 ± 2.14[6,13,15]
					3.20 ± 4.12[6,14]#		3.20 ± 3.52[3,6,14]#		1.50 ± 1.93[6,14,15]
		Intervention[12]	15[1]	6.20 ± 1.94[6]	3.50 ± 2.74[6,13]#	6.10 ± 1.73[3,6]	4.80 ± 3.04[3,6,13]	1.90 ± 2.21[6,15]	1.70 ± 1.83[6,13,15]
					2.40 ± 2.84[6,14]#		3.40 ± 3.75[3,6,14]#		1.30 ± 1.49[6,14,15]
		Control	16[1]	7.60 ± 2.73[6]	4.10 ± 2.80[6,13]#	7.50 ± 2.07[3,6]	5.30 ± 2.39[3,6,13]#	2.70 ± 1.92[6,15]	2.60 ± 2.13[6,13,15]
					3.70 ± 2.71[6,14]#		4.60 ± 2.39[3,6,14]#		2.30 ± 1.89[6,14,15]
Vernia et al. [20]	1995	Intervention	20[16]	N/A	N/A	2.30 ± 0.40[6,17]	1.70 ± 0.60[6,17]#	2.10 ± 9.50[6,18]	1.80 ± 0.70[6,18]#
		Control	20[16]			2.00 ± 0.40[6,17]	1.80 ± 0.60[6,17]	1.80 ± 0.60[6,18]	1.70 ± 0.60[6,18]

[1] number of patients who were included to the study; [2] median (range); [3] scoring of five abnormalities (erythema, edema, friability, granularity, and erosions) from 0 to 2: 0 = absent signs; 1 = mild signs; 2 = severe signs; severe inflammation, maximal scoring = 10; [4] score for acute inflammation: 0–3; for chronic inflammation: 0–3; total histologic score: 0–6; [5] number of patients who completed the study; [6] mean ± standard deviation; [7] change from baseline; [8] mean ± standard error of the mean; [9] endoscopical appearance were each rated on a scale from 0 (normal) to 3 (notably abnormal); [10] histology index were graded on a scale from 0 to 3 for each of the following criteria: cryptitis/abscesses, surface erosions/exudates, polymorphonuclear leucocytes in the lamina propria and glandular mucin depletion; the sum of these scores: maximum=12; [11] treatment with a combination of short chain fatty acids (SCFA); [12] butyrate monotherapy; [13] after 4 weeks; [14] after 8 weeks; [15] histological score assessed the following parameters of acute inflammation: ulceration, crypt abscesses, neutrophilic infiltration of mucosa, epithelial alterations; [16] the number of patients who were included to the study and completed the study; [17] the endoscopic grade was described as: 0 = normal mucosal pattern: 1 = mucosal erythema, slight oedema, red spots; 2 = superficial erosions, friable mucosa with bleeding upon touch, minimum spontaneous bleeding: 3 = marked spontaneous bleeding, severe mucosal ulceration, large amount of mucopurulent discharge; [18] the histological score was graded as follows: from 0 (normal mucosa) to 3 (severe inflammation), according to the degree of goblet cell depletion, inflammatory cell infiltration, superficial epithelium alteration, ulcerations, crypt shape and crypt abscesses; # $p<0.05$ for pre- and post-intervention comparison; N/A: not available.

Table 4. Risk of bias.
Tabela 4. Ryzyko stronniczości.

Study	Year	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Quality
		Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	
Schauber et al. [24]	2000	?	?	+	+	+	+	Fair quality
Breuer et al. [28]	1997	+	?	+	+	+	+	Good quality
Scheppach et al. [29]	1996	?	?	+	?	?	+	Poor quality
Vernia et al. [20]	1995	?	?	+	+	?	+	Poor quality

+ low risk; ? unclear risk; – high risk

28, 29], whereas a statistically significant decrease in the histological score after the intervention period in the SCFA groups was found in only one study [20].

Risk of bias

Table 4 presents the risk of bias of included studies. One study was classified as of good quality [28], one as of fair quality [24] and two as of poor quality [20, 29]. In all studies, allocation concealment was assessed as unclear because it is possible that the participants could foresee assignments due to the specific odor of SCFAs [20, 24, 28, 29].

Discussion

This review aimed to assess the efficacy of SCFAs therapy in IBD and did not document a significant effect of SCFAs enemas on histological and endoscopic scores compared to the control groups. Furthermore, no differences in DAI were reported between the intervention groups and the control groups. Although there were no differences in any of the parameters assessed compared to the control groups, researchers noted significant differences between pre- and post-intervention values of DAI [28, 29] as well as the endoscopic score [24, 28, 29] both in the SCFA groups and the control groups. In addition, one study reported a decrease in the histological score after the intervention period in the SCFA group [20]. Our results are in contrast to a previous study, which reported that SCFA enemas were equally effective in the improvement of endoscopic and histologic scores as corticosteroid and 5-ASA enemas [23].

Several factors might impact on the obtained results. First, it is possible that the effect of SCFA enemas might be different in UC and CD patients, but most studies included in this systematic review were performed in UC patients [20, 28, 29]. Therefore, we could not verify this hypothesis. In addition, it was suggested that the duration of the current episode of diseases might affect the response to SCFA therapy. Indeed, Breuer et al. [28] reported that patients with a relatively short current episode of colitis (less than 6 months) responded better to SCFA than to placebo (48% *vs.* 18%). These patients also had larger but statistically non-significant decreases in the DAI. Breuer et al. [28] also found that the baseline DAI and sex were related to global response in the SCFA group and multiple logistic regression analysis indicated that these factors contributed independently to the response of therapy. However, the volume of enemas was similar in all studies and there is no evidence that 200 ml dosages (2 x 100 ml/d) [20, 28] were more effective than 120 ml (2 x 60 ml/d) [24, 29]. Besides, it seems that the composition and concentrations of SCFA enemas did not affect the response to the therapy [20, 24, 28, 29]. In addition, it should be noted that during SCFAs interventions, most patients remained on oral mesalazine, sulfasalazine or other oral medications [20, 28, 29]. As 5-ASA is one of the most common medications used in IBD treatment, it is supposed that many patients continue taking them in the long-term.

The duration of intervention might also play a role in the efficacy of SCFAs. Scheppach et al. [29] reported a decrease in DAI and endoscopic score after 4–8 weeks of intervention. In the uncontrolled intervention study, Breuer et al. [18] also noted clinical improvements between the third and sixth week of therapy. Nonetheless, rectal irrigation is not the treatment method preferred by IBD patients, with over 30% of participants failing to complete the five weeks of treatment despite no significant side effects reported. The only observed side effect was occasional minor anal irritation caused by the enema tip [28]. In other studies, two patients had severe leakage problems [24], and one reported tenesmus [29]. Furthermore, 30% of patients were unable to retain over half of the enemas for at least 30 minutes [29]. These data suggest that longer interaction between SCFAs and mucosa may be an important indicator of efficacy. Furthermore, research using an oral encapsulated form to release SCFAs in the inflamed area is required.

One of the strongest factors affecting SCFAs levels in the intestinal lumen is diet. Dietary

fiber as a substrate for intestinal bacteria indirectly increases the content of SCFAs in the digestive tract up to 400–600 mM per day in the cecum [30]. Furthermore, the amount and type of fiber have an impact on the rate and ratio of SCFA production. A high fermentability fraction of fiber, such as pectin, relates to greater SCFA production *in vitro* [31]. SCFAs decrease pH in the intestinal lumen via butyrate-producing bacteria belonging to the *Firmicutes* phylum, which comprise 20% of the human fecal microbial population at pH 5.5. In the distal part of the colon where the pH is higher, acetate- and propionate-producing bacteria replace the butyrate producers [32]. The modification in the acidity of the intestines may also influence the transport of SCFAs from the lumen to the colonocytes [33]. The acidity of enemas was usually adjusted to the pH of the colon and rectum (pH=7.0), with only Scheppach et al. [29] using an enema with a lower pH (pH=5.5). However, the effect of different pH of SCFAs enemas on the effectiveness of IBD treatment is unknown.

This systematic review has some limitations. Firstly, the number of included studies was relatively small, with most research involving relatively small groups of patients. In addition, most studies were performed in the 1990s. Moreover, there were many variations between the studies, e.g., patients differed in ethnicity, age, sex, type and activity of the disease, methods of treatment, and the length of the intervention period. Besides, during the intervention, most study participants also took other medications, such as mesalazine and corticosteroids, which could affect the obtained results both in the intervention groups and the control groups. Of note, the conducted research concerned only adults, while it is possible that intervention among children would yield different results. It is also important to note that all studies assessed the effect of SCFA enemas administration. The therapeutic effect of oral SCFAs capsules on IBD has not been studied. Furthermore, data on long-term follow-up was limited, so it is not possible to determine the long-term effectiveness of the therapy. It may be due to technical issues related to enema administration, which is quite burdensome for patients, as the irrigation is time-consuming and requires patients to be disciplined, thereby impacting patient compliance.

Nonetheless, the strengths of this review are the detailed characteristics of the included studies and study populations. Every study included in the review was comprehensively analyzed, taking into account the heterogeneity of the included trials. Furthermore, it should be emphasized that this is one of the first systematic reviews that comprehensively compares the effect of SCFAs therapy on DAI, histological and endoscopic scores in patients with IBD. Also, this review was written based on a search of the four most extensive available databases, that is PubMed, Scopus, Web of Science, and Cochrane.

Conclusion

Currently, there is no evidence that the administration of SCFAs enemas had a positive impact on disease activity index as well as the endoscopic and histological scores of patients with IBD. However, the available data are limited and most studies were performed on small groups of patients.

References

1. Yamamoto-Furusho JK. Clinical epidemiology of ulcerative colitis in Mexico: a single hospital-based study in a 20-year period (1987–2006). *J Clin Gastroenterol*. 2009; 43(3): 221–224. doi: 10.1097/MCG.0b013e31817a76b4.
2. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology*. 2010; 139(4): 1147–1155. doi: 10.1053/j.gastro.2010.06.070.
3. Kamm MA. Rapid changes in epidemiology of inflammatory bowel disease. *Lancet*. 2018; 390(10114): 2741–2742. doi: 10.1016/S0140-6736(17)32669-7.
4. Dulai PS, Singh S, Ohno-Machado L, Sandborn WJ. Population health management for inflammatory bowel disease. *Gastroenterology*. 2018; 154(1): 37–45. doi: 10.1053/j.gastro.2017.09.052.
5. de Lange KM, Barrett JC. Understanding inflammatory bowel disease via immunogenetics. *J Autoimmun*. 2015; 64: 91–100. doi: 10.1016/j.jaut.2015.07.013.
6. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H; IBD guidelines eDelphi consensus group, Gaya DR, Iqbal TH, Taylor SA, Smith M, Brookes M, Hansen R, Hawthorne AB. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019; 68 (Suppl 3): 1–106. doi: 10.1136/gutjnl-2019-318484.
7. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho GT, Satsangi J, Bloom S; IBD Section of the British Society of Gastroenterology.. Guidelines for the management of inflammatory bowel disease in adults. *Gut*. 2011; 60(5): 571–607. doi: 10.1136/gut.2010.224154.
8. Kamm MA, Sandborn WJ, Gassull M, Schreiber S, Jackowski L, Butler T, Lyne A, Stephenson D, Palmen M, Joseph RE. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology*. 2007; 132(1): 66–75. doi: 10.1053/j.gastro.2006.10.011.
9. Modigliani R, Mary J-Y, Simon J-F, Cortot A, Soule JC, Gendre JP, Rene E. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives. *Gastroenterology*. 1990; 98(4): 811–818. doi: 10.1016/0016-5085(90)90002-i.
10. Sands BE, Peyrin-Biroulet L, Loftus EV, Danese S, Colombel JF, Törüner M, Jonaitis L, Abhyankar B, Chen J, Rogers R, Lirio RA, Bornstein JD, Schreiber S; VARSITY study group. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med*. 2019; 381 (13): 1215–1226. doi: 10.1056/NEJMoa1905725.
11. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, Adedokun OJ, Li K, Peyrin-Biroulet L, Van Assche G, Danese S, Targan S, Abreu MT, Hisamatsu T, Szapary P, Marano C; UNIFI Study Group. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2019; 26; 381(13): 1201–1214. doi: 10.1056/NEJMoa1900750.
12. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J Lipid Res*. 2013; 54(9): 2325–2340. doi: 10.1194/jlr.R036012.

13. Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. *Adv Immunol*. 2014; 121: 91–119. doi: 10.1016/B978-0-12-800100-4.00003-9.
14. Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. *Respirology*. 2006; 11(1): 54–61. doi: 10.1111/j.1440-1843.2006.00784.x.
15. Basu A, Devaraj S, Jialal I. Dietary factors that promote or retard inflammation. *Arterioscler Thromb Vasc Biol*. 2006; 26(5): 995–1001. doi: 10.1161/01.ATV.0000214295.86079.d1.
16. Huda-Faujan N, Abdulamir AS, Fatimah AB, Anas OM, Shuhaimi M, Yazid AM, Loong YY. The impact of the level of the intestinal short chain Fatty acids in inflammatory bowel disease patients versus healthy subjects. *Open Biochem J*. 2010; 4: 53–58. doi: 10.2174/1874091X01004010053.
17. Vogt SL, Peña-Díaz J, Finlay BB. Chemical communication in the gut: effects of microbiota-generated metabolites on gastrointestinal bacterial pathogens. *Anaerobe*. 2015; 34: 106–115. doi: 10.1016/j.anaerobe.2015.05.002.
18. Breuer RI, Buto SK, Christ ML, Bean J, Vernia P, Paoluzi P, Di Paolo MC, Caprilli R. Rectal irrigation with short-chain fatty acids for distal ulcerative colitis: Preliminary report. *Digest Dis Sci*. 1991; 36(2): 185–187. doi: 10.1007/BF01300754.
19. Patz J, Jacobsohn WZ, Gottschalk-Sabag S, Zeides S, Braverman DZ. Treatment of refractory distal ulcerative colitis with short chain fatty acid enemas. *Am J Gastroenterol*. 1996; 91(4): 731–734.
20. Vernia P, Marcheggiano A, Caprilli R, Frieri G, Corrao G, Valpiani D, Di Paolo MC, Paoluzi P, Torsoli A. Short-chain fatty acid topical treatment in distal ulcerative colitis. *Aliment Pharmacol Ther*. 1995; 9(3): 309–313. doi: 10.1111/j.1365-2036.1995.tb00386.x.
21. Tarrerias LA, Millecamps M, Alloui A, Beaughard C, Kemeny JL, Bourdu S, Bommelaer G, Eschalier A, Dapoigny M, Ardid D. Short-chain fatty acid enemas fail to decrease colonic hypersensitivity and inflammation in TNBS-induced colonic inflammation in rats. *Pain*. 2002; 100(1–2): 91–97. doi: 10.1016/s0304-3959(02)00234-8.
22. Kripke SA, Fox AD, Berman JM, Settle RG, Rombeau JL. Stimulation of intestinal mucosal growth with intracolonic infusion of short-chain fatty acids. *JPEN J Parenter Enteral Nutr* 1989; 13(2): 109–116. doi: 10.1177/0148607189013002109.
23. Senagore AJ, MacKeigan JM, Scheider M, Ebrom JS. Short-chain fatty acid enemas: a cost-effective alternative in the treatment of nonspecific proctosigmoiditis. *Dis Colon Rectum*. 1992; 35(10): 923–927. doi: 10.1007/BF02253492.
24. Schauber J, Bark T, Jaramillo E, Katouli M, Sandstedt B, Svenberg T. Local short-chain fatty acids supplementation without beneficial effect on inflammation in excluded rectum. *Scand J Gastroenterol*. 2000; 35(2): 184–189. doi: 10.1080/003655200750024371.
25. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PLoS Med*. 2009; 6(7): e1000097. doi: 10.1371/journal.pmed.1000097.
26. Furlan AD, Pennick V, Bombardier C, Bouter L; Editorial Board of the Cochrane Collaboration Back Review Group. Updated method guidelines for systematic reviews in the Cochrane back review group. *Spine*. 2009; 34(18): 1929–1941. doi: 10.1097/01.BRS.0000065484.95996.AF.
27. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane handbook for systematic reviews of interventions version 6.0. Cochrane; 2019. Available from: www.training.cochrane.org/handbook. Accessed on 27 March 2020.
28. Breuer RI, Soergel KH, Lashner BA, Christ ML, Hanauer SB, Vanagunas A, Harig JM, Keshavarzian A, Robinson M, Sellin JH, Weinberg D, Vidican DE, Flemal KL, Rademaker AW. Short chain fatty acid rectal irrigation for left-sided ulcerative colitis: a randomised, placebo controlled trial. *Gut*. 1997; 40(4): 485–491. doi: 10.1136/gut.40.4.485.
29. Scheppach W. Treatment of distal ulcerative colitis with short-chain fatty acid enemas a placebo-controlled trial. German-Austrian SCFA Study Group. *Digest Dis Sci*. 1996; 41(11): 2254–2259. doi: 10.1007/BF02071409.
30. Bergman EN. Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. *Physiol Rev*. 1990; 70(2): 567–590. doi: 10.1152/physrev.1990.70.2.567.
31. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. *Physiol Rev*. 2001; 81(3): 1031–1064. doi: 10.1152/physrev.2001.81.3.1031.
32. Walker AW, Duncan SH, McWilliam Leitch EC, Child MW, Flint HJ. pH and peptide supply can radically alter bacterial populations and short-chain fatty acid ratios within microbial communities from the human colon. *Appl Environ Microbiol*. 2005; 71(7): 3692–3700. doi: 10.1128/AEM.71.7.3692-3700.2005.
33. Cook SI, Sellin JH. Review article: short chain fatty acids in health and disease. *Aliment Pharmacol Ther*. 1998; 12(6): 499–507. doi: 10.1046/j.1365-2036.1998.00337.x.