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Comparison of short-chain fatty acid (SCFA) patterns in children with and without Hirschsprung's disease

Riana Pauline Tamba*[1], Thomas Aribowo Kristianto[2], Yusra Yusra[3]

[1]*Division of Pediatric Surgery, Department of Surgery, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*
[2]*Department of Surgery, Cipto Mangunkusumo Hospital, Jakarta, Indonesia*
[3]*Department of Clinical Pathology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*

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***Corresponding Author**: Riana Pauline Tamba, rianatamba@gmail.com

ABSTRACT

Aims: Hirschsprung's disease (HD) is a congenital gastrointestinal anomaly that causes morbidity and increases the risk of mortality. The increased risk of infection in HD is related to several factors, including dysbiosis of the intestinal microbiota, which plays an important role in maintaining intestinal function through the production of short-chain fatty acids (SCFAs). This study aimed to determine the differences in SCFA levels in children with HD and children without HD.

Methods: This study used an observational analytic cross-sectional design. The subjects were pediatric patients treated at Cipto Mangunkusomo Hospital from January to June 2024 who met the inclusion and exclusion criteria. A total of 17 pediatric patients were included, consisting of 9 children with HD and 8 children without HD. Fecal SCFA levels were analyzed and compared between the two groups.

Results: SCFA levels in children with HD (2.4±1.6) were significantly lower than in children without HD (7.9±2.4) ($p<0.05$). There were no statistically significant differences ($p>0.05$) between the HD group (n=9) and the non-HD group (n=8) in individual SCFA components, including butyrate, propionate, valerate, and acetate levels.

Conclusion: Children with HD have significantly lower total fecal SCFA levels compared to children without HD, while no significant differences were found in individual SCFA components.

Keywords: Hirschsprung's disease, short-chain fatty acids, Hirschsprung-associated enterocolitis

INTRODUCTION

Hirschsprung's disease (HD) is a congenital gastrointestinal disorder caused by the absence of ganglion cells in the submucosal and myenteric plexuses, resulting in loss of normal intestinal peristalsis and functional bowel obstruction.[1] The incidence of HD has been reported to range from approximately 1 in 5,000 to 1 in 10,000 live births.[2] This condition is associated with substantial morbidity and a risk of mortality, particularly due to complications such as Hirschsprung-associated enterocolitis (HAEC), which remains a life-threatening condition in affected patients.[3,4] HAEC may occur in 6-60% of patients before definitive surgery and in 25-37% after surgery, with reported mortality rates reaching up to 10%.[3-5]

The pathophysiology of HAEC has not been fully elucidated. Several factors have been implicated, including impaired immune responses, dysfunction of the epithelial barrier, and intestinal dysbiosis.[6] The intestinal microbiota plays an essential role in maintaining gut homeostasis, and one of its key functions is the production of short-chain fatty acids (SCFAs).[7] SCFAs, mainly acetate, propionate, and butyrate, account for approximately 90-95% of SCFAs in the colon and are produced through bacterial fermentation of non-digestible carbohydrates.[7,8] These metabolites serve as an important energy source for colonocytes, contribute to epithelial barrier integrity, and exert anti-inflammatory and immunomodulatory effects.[8,9]

Alterations in SCFA production have been associated with various gastrointestinal and inflammatory conditions. A prospective study by Rao et al.[10] showed that neonates with congenital gastrointestinal anomalies had lower fecal SCFA concentrations compared with healthy infants. Decreased SCFA levels may increase the risk of colonic infection and impair mucosal defense.[8] Demehri et al.[3] reported up to a fourfold reduction in fecal SCFA concentrations in patients

with HD (particularly those with a history of HAEC), supporting the role of dysbiosis and altered microbial metabolism in the pathogenesis of enterocolitis.

Most previous studies remain limited. SCFA concentrations in early life are known to vary with age and dietary factors, with considerable variability during the first year of life.[11] This variability complicates the interpretation of SCFA profiles across different pediatric populations. This study aimed to compare fecal SCFA levels in children with HD and children without HD. By evaluating total SCFA levels and individual SCFA components, this study seeks to provide further insight into the role of altered microbial metabolism in HD and its potential implications for intestinal health and susceptibility to complications. Data on SCFA profiles in children with HD remain limited, particularly in developing countries, highlighting the need for further investigation.

METHODS

This study was conducted with approval from the Ethics Committee of Faculty of Medicine, Universitas Indonesia (Date: 18.12.2023, Decision No: KET-1814/UN2.F1/ETIK/PPM.00.02/2023). The study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment in the study. Patient confidentiality and data anonymity were maintained throughout the study.

This study was an observational analytic study with a cross-sectional design. The study was conducted at Cipto Mangunkusumo Hospital, Jakarta, Indonesia, from January to June 2024. The target population was pediatric patients with HD, and the accessible population consisted of pediatric patients treated at Cipto Mangunkusumo Hospital during the study period.

Subjects were recruited using a consecutive sampling method. A total of 17 pediatric subjects were included in this study, consisting of 9 children with HD and 8 children without HD. The control group consisted of pediatric patients without HD who were treated at Cipto Mangunkusomo Hospital during the study period and fulfilled the inclusion and exclusion criteria. Stool samples for SCFA analysis were collected as part of the study protocol after informed consent had been obtained from parents or legal guardians. The cost of SCFA examination was covered by the research project.

The inclusion criteria were: pediatric patients aged 1 month to 18 years with HD, either before or after definitive surgery (within 28 days postoperatively); and pediatric patients aged 1 month to 18 years without HD or other congenital gastrointestinal diseases. The exclusion criteria were: Patients with other congenital gastrointestinal anomalies; and patients with a history of antibiotic or probiotic use within one month prior to stool sample collection, including patients with recent perioperative antibiotic exposure within that period. Due to the limited number of eligible patients during the study period, a formal sample size calculation was not performed, and the study should be considered exploratory in nature.

Fecal SCFA concentrations were analyzed using gas chromatography–mass spectrometry (GC-MS) at the Laboratorium Prodia Kramat. Stool samples were collected in sterile containers and stored at 4°C until analysis. Prior to analysis, the samples were prepared according to the laboratory protocol, including homogenization, dilution, centrifugation, and derivatization. Quantification of acetate, propionate, butyrate, and valerate was performed using standard calibration curves with internal standards. Quality control procedures were applied throughout the analysis to ensure measurement accuracy and reproducibility.

Statistical Analysis

Data were analyzed using statistical software. Continuous variables were presented as mean±standard deviation for normally distributed data and as median (minimum–maximum) for non-normally distributed data. Comparisons between groups were performed using the Independent t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were presented as n (%) and compared using Fisher's exact test or the Chi-square test, as appropriate. A p value of <0.05 was considered statistically significant.

The primary outcome of this study was the difference in total fecal SCFA levels between children with and without HD. Secondary outcomes included differences in the individual SCFA components, namely acetate, propionate, butyrate, and valerate.

RESULTS

A total of 17 pediatric subjects were included in this study, consisting of 9 children with HD and 8 children without HD. The baseline characteristics of the study subjects are summarized in **Table 1**.

Table 1. Baseline characteristic of the study subjects

Variables	HD (n=9)	Without HD (n=8)	p-value
Age, median (min-max), months	28 (7-168)	24 (6-71)	0.423
Gender			
Male (%)	7 (77.8)	2 (25)	0.057
Female (%)	2 (22.2)	6 (75)	
Exclusive breastfeeding			
Yes (%)	8 (88.9)	8 (100)	1.000
No (%)	1 (10.1)	0 (0)	
Definitive surgical treatment			
Yes (%)	4 (44.4)	0 (0)	0.082
No (%)	5 (55.6)	8 (100)	
HAEC history			
Yes (%)	4 (44.4)	0 (0)	0.082
No (%)	5 (55.6)	8 (100)	
Nutritional status			
Normal (%)	5 (55.6)	8 (100)	0.098
Undernourished (%)	2 (22.2)	0 (0)	
Severely malnourished (%)	2 (22.2)	0 (0)	

HD: Hirschsprung's disease, Min: Minimum, Max: Maximum, HAEC: Hirschsprung-associated enterocolitis

The characteristics analyzed included age, gender, nutritional status, and relevant clinical variables. There were no significant differences between the HD group and the non-HD group in baseline demographic characteristics (p>0.05), indicating that the two groups were comparable at baseline.

The results of fecal SCFA analysis are summarized in **Table 2**. The comparison between the HD group and the non-HD group showed a significant difference in total SCFA levels.

Table 2. SCFA analysis result data

Variables	HD (n=9)	Without HD (n=8)	p value
Total SCFA levels (mg/ml)	2.4±1.6	7.9±2.4	<0.05[a]
Absolute butyrate levels (mg/ml)	0.9±0.3	0.8±0.4	0.921[b]
Butyrate levels (%)	3 (1-25)	8.5 (3-14)	0.481[b]
Propionate levels (%)	7 (1-21)	21.5 (10-24)	0.300[b]
Valerate levels (%)	0.9 (0.2-2.3)	0.4 (0.1-3.6)	0.309[b]
Acetate levels (%)	78.1±15.3	67.5±7.4	0.095[b]

a: Independent t-test analysis, b: Mann-Whitney analysis. Categorical variables are presented as n (%). Normally distributed numerical variables are presented as mean±standard deviation. Non-normally distributed numerical variables are presented as median (minimum–maximum).
SCFA: Short-chain fatty acid, HD: Hirschsprung's disease

The mean total SCFA level in children with HD was 2.4±1.6. This was significantly lower than that children without HD (7.9±2.4) (p<0.05) (**Table 2**). Further analysis of individual SCFA components showed no significant differences between the two groups. There were no significant differences in absolute butyrate levels, butyrate levels, propionate levels, valerate levels, or acetate levels between children with HD (n=9) and children without HD (n=8) (all p>0.05) (**Table 2**).

DISCUSSION

In this study, fecal total SCFA levels in children with HD (2.4±1.6) were significantly lower than in children without HD (7.9±2.4) (p<0.05). This finding is consistent with the study by Liu et al.,[13] who used Mendelian randomization analysis to investigate the association between gut microbiota and HD. The study demonstrated a reduction in *Clostridiaceae* and *Ruminococcus*, which are protective intestinal flora and major producers of SCFAs, thereby predisposing patients with HD to lower SCFA levels. One factor contributing to alterations in gut microbiota diversity is surgical intervention. Previous studies have shown a reduction in gut microbiota diversity in patients with HD after definitive surgery compared with healthy children, with significant differences in the degree of microbial diversity loss depending on the length of colonic resection.[6]

Reduced SCFA levels in children with HD are also associated with a history of HAEC. Demehri et al.[3] reported that fecal SCFA levels were reduced by more than fourfold in children with a history of HAEC, accompanied by changes in SCFA composition, suggesting a complex interaction between colonic metabolism and alterations in gut microbiota. In HAEC, bacterial overgrowth and reduced microbial diversity increased release of inflammatory factors, resulting in intestinal dysmotility which further promotes bacterial overgrowth and perpetuates microbial imbalance. These processes are mediated by intestinal epithelial changes, including reduced production of secretory phospholipase A2 (sPLA2), increased bacterial lipopolysaccharide (LPS) production, and downregulation of TFF3, SPDEF, and KLF4 expression. This would cause a reduction in goblet cells and decreased neutral and acidic mucin secretion therefore weakening the mucosal barrier function.[14]

In the present study, no significant difference was found in absolute butyrate levels between the HD group (0.9±0.3 mg/ml) and the non-HD group (0.8±0.4 mg/ml) (p>0.05). However, the proportion of butyrate tended to be lower in the HD group (3 [1-25]) compared with the non-HD group (8.5 [3-14]). A similar finding was reported by Liu et al.,[13] who observed a reduction in butyrate levels in children with HD, accompanied by a decrease in *Clostridiaceae* abundance. Plekhova et al.[16] further explained that reduced butyrate production in patients with HD may be influenced by increased lysine catabolism, in which lysine serves as an alternative substrate to carbohydrates (the primary substrate for SCFA production). In addition, reduced levels of N-acetylglucosamine and N-acetylneuraminic acid were associated with impaired carbohydrate digestion due to gut microbiota dysbiosis. These findings are in line with previous studies suggesting that characteristic gut microbiota and SCFA profiles in children with HD may contribute to the development of HAEC.[16]

In patients with HD complicated by HAEC, additional metabolic alterations have been reported. This included increased tyrosine catabolism, reduced degradation of trans-4-hydroxy-L-proline (Hyp), and changes in specific volatile compounds. Hyp is a common product of anaerobic proline transformation utilized by gut microbiota, particularly *Clostridium* spp., which are major butyrate producers. Increased Hyp concentrations may indicate a reduction in Hyp-utilizing microbiota and may partly explain the lower SCFA concentrations observed in patients with HAEC.[15] However, these findings differ from those reported by Prato et al.,[17] who performed metagenomic analysis of fecal samples from children with HD with and without HAEC and found increased butyrate production in children with HAEC.

In contrast to other SCFAs, this study found a tendency toward a higher proportion of valerate in the HD group (0.9 [0.2-2.3]) compared with the non-HD group (0.4 [0.1-3.6]). A similar trend was reported by Demehri et al.,[3] who observed increased valerate and isovalerate levels in HD. In addition, the proportion of acetate in this study tended to be higher in children with HD (78.1±15.3) than in children without HD (67.5±7.4). Different results were reported by Chantakhow et al.,[6] who found reduced acetate levels in children with HD compared with butyrate levels. In cases of HAEC, Demehri et al.[3] reported a significant reduction in acetate levels in children with HAEC compared with those with HD without HAEC. Similar findings were also reported by Prato et al.,[17] who demonstrated reduced acetate production due to impaired development of acetate-producing bacterial colonies in children with HAEC.

Limitations

This study has several important limitations. First, the sample size was small, which may limit statistical power and generalizability; therefore, the findings should be interpreted as exploratory. Second, the study included a wide age range, which may have introduced variability in SCFA profiles because gut microbiota composition changes with age. Third, the HD group was heterogeneous, including both pre- and post-operative patients as well as patients with a history of HAEC, all of which may have influenced SCFA levels. Finally, potential confounding factors such as diet, breastfeeding status, and intestinal transit time were not fully controlled.

CONCLUSION

This study demonstrated that children with HD have significantly lower total fecal SCFA levels compared with children without HD. However, no statistically significant differences were observed in individual SCFA components. These findings suggest that alterations in overall SCFA production may be associated with HD, although further studies with larger sample sizes are needed to confirm these results.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with approval from the Ethics Committee of Faculty of Medicine, Universitas Indonesia (Date: 18.12.2023, Decision No: KET-1814/UN2.F1/ETIK/PPM.00.02/2023).

Informed Consent

Informed consent was obtained from a parent or legal guardian. Where appropriate, age-adjusted assent was also obtained from the child. The inclusion of vulnerable populations in this study adhered to national and international ethical guidelines. Extra care was taken to ensure voluntary participation, understanding, and protection of participant dignity and autonomy.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: RPT, TAK, YY; Design: RPT, TAK, YY; Control: RPT, TAK, YY; Data Collection and/or Processing: RPT, TAK, YY; Analysis and/or Interpretation: RPT, TAK, YY; Literature Review: RPT, TAK, YY; Article Writing: RPT, TAK, YY; Critical Review: All Authors.

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