SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Hirschsprung disease associated enterocolitis: a systematic review and meta-analysis

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ABSTRACT

Introduction: Hirschsprung's disease-associated enterocolitis (HAEC) remains a substantial morbidity and mortality risk in Hirschsprung's disease. HAEC is a challenge. Its p athophysiology is still a mystery, and no adequate treatment strategy exists. The aim of the study is to analyse the pre-and post-operative, mortality and complications: strictures, anastomotic leak, constipation and incontinence associated with HAEC.

Materials and Methods: Adjust to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020; this study met all the requirements and was up-to-date. The search approach was online publications between 2013 and 2023 in Pubmed and SagePub. It was decided not to consider review pieces that had already been published and half done. The STATA 18th version was used for meta-analysis.

Results: Our search results included 370 PubMed and 149 SagePub articles. Since 2013, 134 PubMed and nine SagePub articles have been obtained, and seven studies have met the criteria.

Conclusion: Disorders of intestinal motility in the aganglionic segment and accumulation of faeces disrupt the balanced microbiota population, which are factors of pre-operative HAEC. Major congenital anomalies and low birth weight worsen pre-operative HAEC. Pre-operative HAEC can continue and affect the post-operative. Constipation and fecal incontinence are still the main challenges after HSCR surgery.

KEYWORDS:
Hirschsprung disease associated enterocolitis, incidence; etiology, complication

INTRODUCTION

Since the description of Hirschsprung's disease (HSCR) in Berlin in 1886, remarkable discoveries have been made regarding its aetiology, pathophysiology, optimal medical-surgical management and follow-up care. Hirschsprung's disease (HSCR) is characterised by an absence of enteric nervous system (ENS) ganglion cells in the myenteric and submucosal plexuses, failing proximal to distal migration of neural crest cell1 and leading to functional obstruction.[2]

Hirschsprung disease-associated enterocolitis (HAEC) is an inflammatory complication that can present either in the pre- or post-operative period and is associated with increased morbidity and mortality. HAEC is a medical challenge, and the pathogenesis remains poorly understood,[2] and there is no adequate treatment strategy yet.[3] The study aims to analyse pre- and post-operative, mortality, anastomosis stricture, and the leakage, constipation, and incontinence associated with HAEC.

MATERIALS AND METHODS

Protocol

The review adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines, to ensure comprehensive and transparent reporting.

Criteria for Eligibility

This meta-analysis analyses pre- and post-operative, mortality, anastomosis stricture, and the leakage, constipation and incontinence associated with HAEC. The included studies must fulfil the following requirements: 1) The paper must be written in English to determine the best management of HCSR and HAEC. 2) Studies published between 2013 and the initiation of this systematic review are considered relevant.. 3) Only original research articles with a DOI are included. Editorials, submissions without a DOI, previously published review articles, and entries that are essentially identical to journal papers already published are excluded.[4]

Search Strategy

We used "Hirschsprung disease associated enterocolitis" and "Hirschsprung disease" as keywords. The search for studies to the PubMed and SagePub databases by inputting the words: (("Hirschsprung"[MeSH Subheading] OR "enterocolitis"[All Fields] OR "Hirschsprung enterocolitis"[All Fields]) AND ("Hirschsprung"[All Fields] OR " Hirschsprung disease"[All Fields]) AND ("enterocolitis"[MeSH Terms] OR ("enterocolitis"[All Fields]) OR ("Hirschsprung associated enterocolitis"[All Fields]) AND "incidence of Hirschsprung"[All

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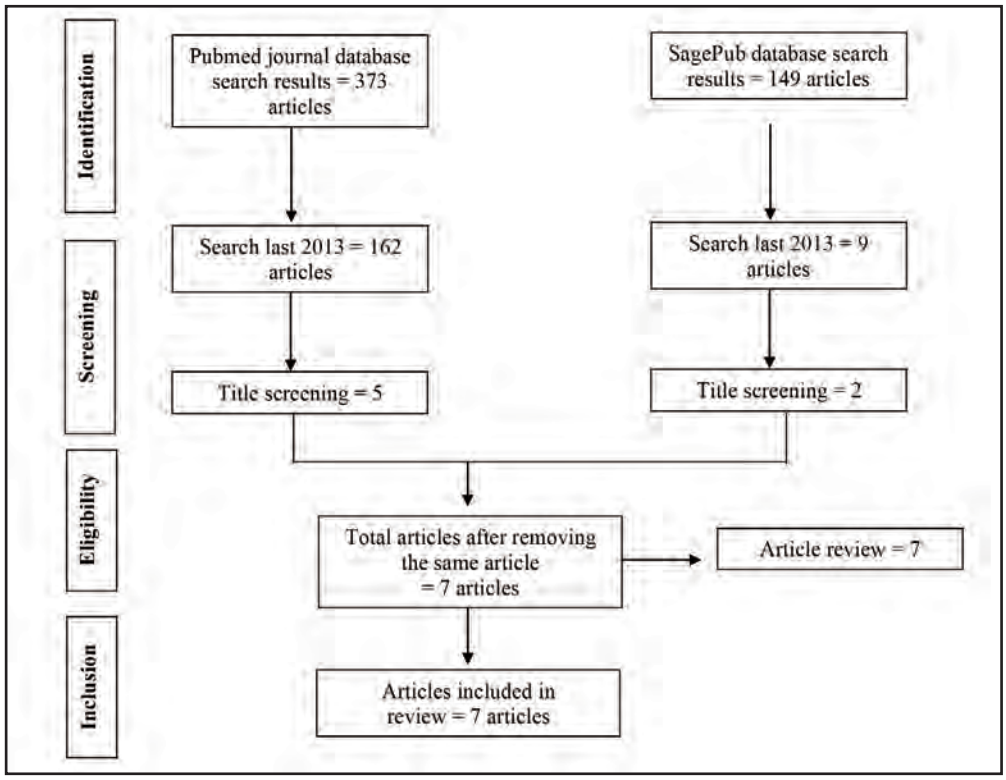


Fig. 1: Article search flowchart.

Fields]) OR ("prevalence of Hirschsprung"[All Fields]) OR ("Hirschsprung mechanism"[All Fields]) OR ("mechanism of Hirschsprung"[All Fields]) AND "treatment of Hirschsprung "[All Fields])) AND ("treatment"[All Fields]) AND (clinicaltrial[Filter])) used in searching the literature. [4]

Data Retrieval

After reading the abstract and the title, the authors examined the studies to determine the inclusion criteria, decided on previous research to use as sources and selected those for the article. The conclusions of this selected previous study followed the same trend, were written in English, and could not be seen in publication.[4]

For the systematic review, inclusion criteria were meticulously defined to narrow the results to only those studies pertinent to the search. Studies that did not meet these predefined criteria were excluded. The findings from the included studies will be subjected to thorough analysis. The following data were extracted: study titles, authors, publication dates, locations, study activities, and parameters.[4]

Quality Assessment and Data Synthesis

Each author reviews the titles and abstracts of the studies to determine their eligibility for further exploration. This review process aligns with the purpose of the systematic review, encompassing assessment and evaluation criteria. Previous studies that meet these criteria are included in the review.[4]

Statistical Analysis

Statistical analysis was conducted using the STATA 18th version. The "metathesis" command pooled the prevalence of single-proportion outcomes (i.e., pre-operative, post-operative, mortality, anastomosis stricture, anastomosis leakage, incontinence, and constipation in HAEC). The "proportion" command was used to compute the effect size of each study. Cochrane's Q and I2 tests added the pooled estimations variation and heterogeneity, respectively, with the p-value < 0.05 considered statistically significant. A fixed effect model was employed to calculate the pooled prevalence. The random effects model estimated the pooled prevalence if the heterogeneity was higher than 50%; otherwise, the fixed effect model was used. The sequentially omitting individual studies with the "metaninf" command were conducted using sensitivity analyses. The pooled mean estimate without it was not within the 95% CI bounds of the overall mean and was considered influential in the study. The result was visualised and evaluated publication bias by forest-plot using the "forest-plot" command.

This study was approved by the Faculty of Medicine and Health, Lambung Mangkurat University Research Ethics Commission N0: 032/KEPK-FKIK ULM/EC/III/2024.

RESULTS

Study Characteristics

In the database, there were 373 PubMed and 149 SagePub articles. In 2013, we found 162 PubMed and nine SagePub articles. We collected seven papers, five from PubMed and two from SagePub, that met the criteria.

Le-Nguyen et al.,[5] showed that other congenital malformations significantly risk developing pre-operative

HAEC (Odds Ratio, OR: 2.63; 95% Confidence Intervale, 95%CI: 1.11, 6.24)). Low-birth-weight patients with pre-operative HAEC (OR: 0.48; 95%CI: 0.25, 0.93). Post-operative intestinal obstruction is significantly associated with pre-operative HAEC (OR: 8.2, 95%CI: 3.18, 21.13). Patients with earlier pull-throughs did not have a lower risk of developing post-operative HAEC.

Parahita et al.,[6] showed that 100 patients (71 Soave vs. 29 Duhamel, p=0.62) had higher significant HAEC in the Duhamel than in the Soave group (28% vs. 10%, respectively, p=0.03). HAEC following pull-through had a substantial association with pre-operative enterocolitis (p=2.0×10-4), and the long-segment aganglionosis had a higher risk of HAEC to short-segment HSCR after Soave pull-through (p=0.015).

Chung et al.,[7] showed that the overall incidence of HAEC was 20.8% (n=20), and 65.0% (n=13) of HAEC occurred within the first year of operation. Three risk factors for HAEC were identified: 1) Presence of other major anomalies (OR: 1.43; 95%CI 1.12, 2.32); (2) Defunctioning stoma (OR: 2.28; 95%CI: 1.47, 3.23); (3) Extension of aganglionosis (OR: 1.89; 95%CI 1.05, 3.19). A significant association of HAEC with pre-operative defunctioning stoma (OR: 1.81, 95%CI 1.08, 3.22) and extension of aganglionosis to the sigmoid colon (OR: 1.91; 95%CI: 1.37, 2.98).

Adiguzel et al.[8] showed that vomiting and abdominal distension were the most common symptoms in 43 boys vs. seven girls at a mean age of 3 months (range 0 to 96 months). Barium enema, anorectal manometry and rectal biopsy were the most widely used; one patient underwent laparotomy with biopsy. The enteral feeding started at 2.2±1.1 days, and the follow-up period was 26.7±20.8 months. Perianal excoriation, enterocolitis, anastomotic stricture, soiling, recurrent constipation, prolapse of the pull-through colon, anastomosis leak and rectovestibular fistula were the post-operative complications.

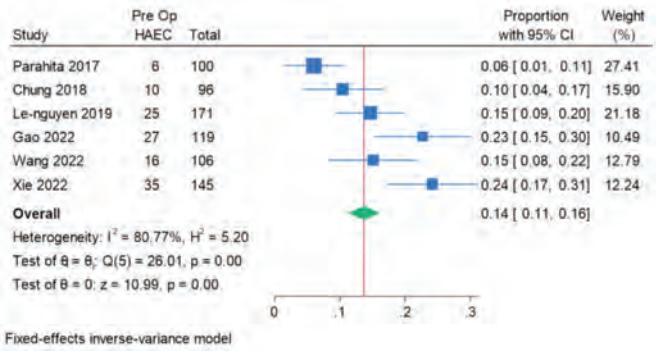
Gao et al.,[9] showed that 119/154 patients were followed up successfully. Post-operative, 53 patients had complications, and 66 patients had no complications. HAEC (33), faecal incontinence (22) and constipation (8) patients were complications. There were no significant differences in operative age, gender, pre-operative HAEC or haemoglobin levels between the Soave, modified Soave, laparoscopic and modified Duhamel operations. However, there were significant differences in the risk of post-operative HAEC in surgical procedures, serum albumin level, clinical classification and one- or two-stage operation (p<0.05).

Wang et al.,[10] showed that 106 patients were discharged 5-7 days after the operation, 150 (100-190) minutes of surgery median time and 6 (3-10) ml was the median bleeding volume. The post-operative daily defecation frequency was 4-11 times (short-term), 3-7 times (within 6 months), and 2-3 times (after 6-12 months). Anastomotic leakage in two, perianal dermatitis in 13, anastomotic stenosis in four, adhesive bowel obstruction in two, enterocolitis in 16, soiling in 11, and constipation recurrence in three cases were post-operative complications.

Xie et al.,[11] showed that pre- and post-operative HAEC incidence was 24.1% and 20.7%, respectively, in 145 patients. The post-operative HAEC in the first year after Soave occurred in more than 90% of patients. Long-segment aganglionosis was the risk factor of pre-operative HAEC (OR: 5.8; 95%CI: 2.4, 14.2) and was significantly associated with post-operative HAEC (OR: 4.2; 95%CI: 1.6, 10.8).

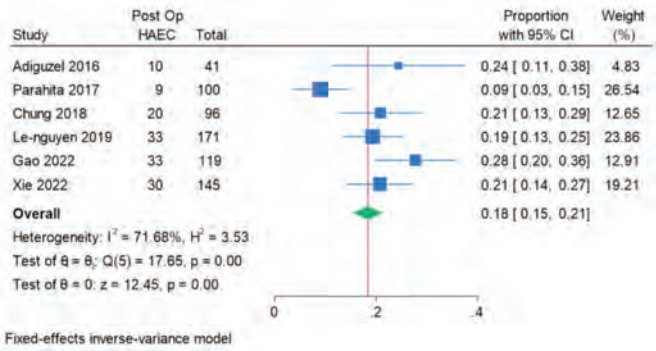
This meta-analysis of this pooled study examines the prevalence of a single proportion of outcomes in pre-operative, post-operative, mortality, anastomosis stricture, anastomosis leakage, incontinence and constipation in HAEC. The patients evaluated 737 for pre-operative HAEC, 672 for post-operative HAEC and 408 for HAEC mortality. Three hundred fifty-seven for anastomosis stricture and 212 for anastomosis leak.

Pre-operative Hirschsprung Associated Enterocolitis



A total of 119 among 737 patients experienced pre-operative HAEC. The overall pooled prevalence of pre-operative HAEC is 0.14 (95%CI: 0.11, 0.16), Cochran Q test, p=0, I^2=80.77%. One hundred twenty-two patients (14%) developed pre-operative HAEC. The 95% confidence interval (CI) of 0.11-0.16 indicates that the actual prevalence in the population is 11% and 16%. A p-value of 0 indicates significant heterogeneity and prevalence among different studies, which is more critical than expected. An I2 value of 80.77% suggests a very high level of heterogeneity.

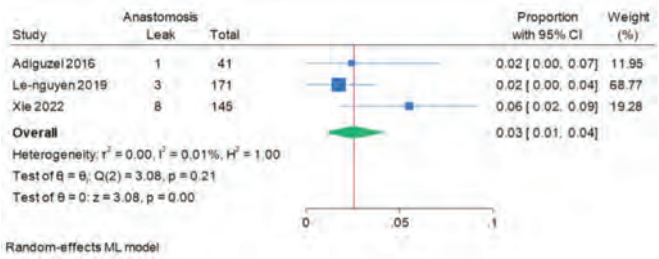
Post-operative Hirschsprung Associated Enterocolitis



A total of 135 among 672 patients experienced post-operative HAEC. The post-operative HAEC overall prevalence was 0.18 (95%CI: 0.15, 0.21), Cochran Q test, p=0, I^2=71.68%. One hundred thirty-six patients developed post-operation HAEC. The prevalence was 18% (95%CI: 0.15, 0.21), with a 95% probability that the actual prevalence in the population lies

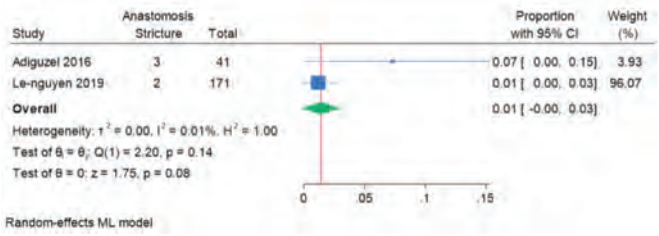
between 15% and 21%. A p-value of 0 indicates significant heterogeneity and prevalence among different studies, which is more critical than expected. I^2=71.68% suggests a high level of heterogeneity.

Anastomosis Leakage in HAEC



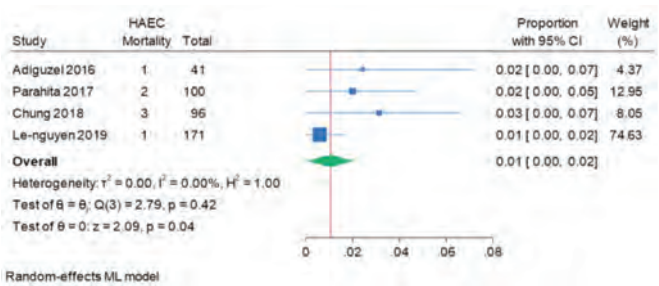
A total of 12 among 357 patients were assessed for anastomosis leak. The overall pooled prevalence is 0.03 (95%CI: 0.01, 0.04), using the Cochran Q test, p=0.21, and I^2=0.01%. Twelve patients were assessed for anastomosis leak. The prevalence is 3%, and a 95% probability that the prevalence of anastomosis leaks in the population between 1% and 4%. A p-value of 0.21 indicates no significant heterogeneity, and the variability in anastomosis leak prevalence among different studies is not more significant than expected. An I^2 value of 0.01% suggests virtually no observed heterogeneity, indicating that the prevalence rates of anastomosis leaks are highly consistent across different studies.

Anastomosis Stricture HAEC



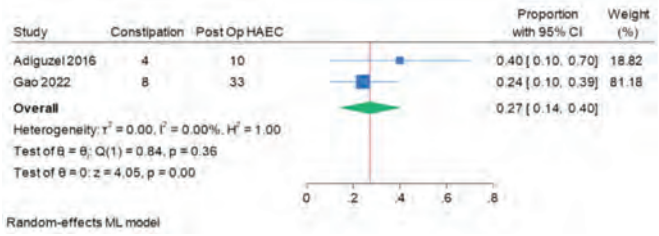
Anastomosis stricture was assessed in five out of 212 patients. The overall pooled prevalence is 0.01 (95%CI: 0.00, 0.01), Cochran Q test, p=0.14, I^2=0.01%. Five patients who experienced an anastomosis stricture were evaluated, and the prevalence is 1%. There is a 95% probability that the anastomosis stricture in the population lies between 0% and 1%. The negative lower bound of the CI was statistically effective at 0%. A p-value of 0.14 indicates no significant heterogeneity, and the variability in anastomosis stricture prevalence among different studies is insignificant. An I^2 value of 0.01% suggests no heterogeneity and is highly consistent across different studies.

HAEC Mortality



The mortality rate of HAEC was seven among 408 patients. The prevalence of HAEC mortality is 0.01 (95%CI: 0.00, 0.02), Cochran Q test, p=0.42, I^2=0%. The mortality prevalence is 1%, and there is a 95% probability that the population lies between 0% and 2%. The negative lower bound of the CI was statistically effective at 0%. A p-value of 0.42 indicates no significant heterogeneity. An I^2 value of 0% suggests no observed heterogeneity, indicating that the mortality rates are consistent across different studies.

Constipation of Post-operative HAEC



Constipation was assessed in 12 patients from 43 post-operative HAEC. The overall pooled prevalence is 0.27 (95%CI: 0.14, 0.40), Cochran Q test, p=0.36, I^2=0%. 12 out of 43 patients were assessed for constipation. The overall pooled prevalence is 27%. There is a 95% probability prevalence of constipation between 14% and 40% in this population. A -- value of 0.36 indicates no significant heterogeneity, and the variability in constipation prevalence among different studies is not more significant. An I^2 value of 0% suggests no observed heterogeneity, indicating that the prevalence rates are consistent across different studies.

Faecal Incontinence of Post-operative HAEC

Only one study assessed faecal defecation; 22 among 33 post-operative HAEC underwent faecal incontinence.[9]

Based on a meta-analysis of these five variables. The pre-and post-operative HAEC variables had Cochran Q test value, p=0, and heterogeneity test I^2 value >50%. The pooled prevalence was significant for the entire study and had heterogeneous data. Meanwhile, HAEC mortality, HAEC anastomosis leakage, and HAEC stricture anastomosis have a p>0.05 and an I^2 value <50%. The pooled prevalence is insignificant in the study and has low data heterogeneity.

DISCUSSION

The pathogenesis of HAEC remains poorly understood, but intestinal dysmotility, dysbiosis, impaired mucosal defence and intestinal barrier function play a significant role. Severe HAEC is a potentially lethal complication of HSCR. HAEC's classical variable clinical presentation is fever, lethargy, abdominal distention, foul-smelling, and explosive diarrhoea, which can occur pre- and post-operatively.[12]

Pre-operative Hirschsprung Associated Enterocolitis

Peristalsis disruption in the aganglionic segment, accumulation of faeces, decreased secretion of immunoglobulin-A and immature mucosa, abnormal mucin secretion, leukocyte dysfunction, and abnormal gut microbiota, which will result in pre-operative HAEC. Local and systemic inflammatory responses and long-segment

aganglionic facilitate the development of HAEC via bowel obstruction and increase intraluminal pressure, lead bacterial stasis, overgrowth, and translocation.[5] Microbiota dysbiosis is essential pathogenesis of HAEC.[13] Age at diagnosis correlates to HAEC incidence, and severe HAEC induces thymic involution, B lymphocyte suppression, and splenic lymphopenia. An immunity deficiency in Trisomy 21, significant cardiac anomaly induced pre-operative HAEC.[5] The age at surgery did not correlate with post-operative HAEC.[14]

Impaired mucosal defence in HSCR correlated with the role of secretory immunoglobulin A (sIgA). The transfer of sIgA across the gastrointestinal wall is impaired in HSCR despite increased sIgA levels in the lamina propria plasma cells and decreased in those with HAEC. The production and transport of intestinal mucins may be abnormal in HSCR and may have a potential role in the pathogenesis of HAEC. MUC-2 is the predominant mucin expressed in humans, and it can prevent bacterial translocation across the intestinal wall.[15]

Pre-operative incidence is 6-60%, while post-operative incidence is 25-42%. HAEC mortality is 5-50%, with higher prevalence in the neonatal period before definitive surgical correction. Mortality rates have declined to less than 1% after surgical and medical care. HAEC is reported as the HSCR symptom in up to 25% of infants. HAEC with bowel perforation in the neonatal period was the most common complication due to increased luminal pressure, transmural inflammation and vascular accidents leading to ischemia and perforation.[12]

Post-operative Hirschsprung Associated Enterocolitis

HAEC is a severe complication after an operation, including a pull-through. Laparotomy pull-through showed a lower HAEC incidence than trans-anal or laparoscopy.[5] The age at surgery did not correlate with post-operative HAEC.[8,14]

Diverting ostomy before corrective pull-through can be considered in the decompensating neonate with long-segment HCSR to lower failure rates of rectal wash-outs. Diversion ostomy may not entirely resolve HAEC, but it does improve the patient's clinical status and quality of life.[16] HAECs still develop after surgical correction or ostomy diversion, indicating the presence of an intrinsic defect at the level of the enteric nervous system that causes dysmotility,[15] prolonged dysbiosis, impaired mucosal defenses and bacterial overgrowth inside the mucosa.[13] Genetic factors, allergies can trigger post-operative HAEC.[10]

HAEC Anastomosis Leakage and Stricture

HAEC is a non-optimal condition and the main factor in anastomotic leakage. Immediate rectal wash-out, optimisation and diversion of the colostomy benefit recovery, and stage surgery are recommended.[9]

Anastomotic stenosis is commonly found in the distal cuff after mucosectomy8 and is treated with a dilation program. Post-operative stenosis increases the incidence of HAEC.[10]

HAEC Mortality

HAEC mortality is between 5-50% depending on the type of infection and age. Pre-operative HAEC in premature babies and major congenital abnormalities is a significant factor in mortality. Prophylactic enterostomy, adequate pull-through, rectal irrigation and close post-operative follow-up are recommendations in severe HAEC.[14]

Constipation and Fecal Incontinence of Post-operative HAEC

Faecal incontinence and constipation are necessary and common complications after a definitive pull-through. The incidence of constipation is relatively high after SOAVE. Mucosectomy to the peritoneal reflection and short cuff increases the risk of pelvic floor injury to nerves and internal sphincter. The sub-epithelium anal canal, colonic motility, anal sphincter and anorectal sensation are the main factors in faecal continence. TEPT reduces the risk of soiling compared to SOAVE.[9]

Limitation of the study was that it did not discuss the molecular biology of HAEC as an essential factor. The following HAEC further studies promising research areas, including intestinal microbiota analysis, personalisation therapy, stem cell study to restore the motor function of the aganglionic bowel, and treatments for colonic mucus barrier properties to prevent the onset of enterocolitis in HSCR.

CONCLUSION

Impairment of bowel motility in the aganglionic part and faecal accumulation causes dysbiosis microbiota, which are factors of pre-operative Hirschsprung's disease-associated enterocolitis (HAEC). Major congenital anomalies and low birth weight worsen pre-operative HAEC. Pre-operative HAEC can continue and affect post-operative. Constipation and Fecal Incontinence are still the main challenges after HSCR surgery.

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