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Novel and Alternative therapies for Childhood constipation

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ABSTRACT

Constipation is a worldwide problem that affects many children. Treatment of constipation is largely based on clinical experience rather than on evidence based controlled clinical trials. Stool softeners and cathartics in combination with behavioral interventions constitute the programs most commonly used to facilitate painless and frequent defecation. Long-term treatment is needed in most cases and approximately 30% of children beyond puberty continue to struggle with symptoms of constipation, such as infrequent, painful evacuation of stools and fecal incontinence. Not surprisingly, chronicity of these bowel complaints may cause significant interference with the child’s emotional growth and development. Development of new therapeutic strategies is necessary in order to treat these challenging patients more effectively. This review provides an overview of novel and alternative therapies, such as new drugs, surgery and probiotics, that are currently being proposed for the treatment of childhood chronic constipation.
INTRODUCTION

Mineral oil, polyethylene glycol, lactulose, bisacodyl, senna and milk of magnesia are just a few examples of the frequently prescribed compounds for the management of childhood constipation. What they all have in common is that they are generally recommended based on clinical practice or experience with little evidence of long term efficacy. Very few large, double-blind, randomized, controlled studies have been performed in children with chronic constipation, a finding which should be surprising considering that constipation is the chief complaint in 3-5% of visits to pediatricians and represents 10-25% of referrals to pediatric gastroenterologist.\(^1\) Moreover, constipation is a worldwide problem with a prevalence ranging from 0.7% to 29.6% both in Western and non-Western countries.\(^2\)

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recently issued a clinical practice guideline to evaluate and manage constipation in infants and children. Their recommendation consisted of education, disimpaction, maintenance therapy with diet changes and/or medication use and behavioral modification.\(^3\) Although these measures are effective in the majority of children, a sizable proportion needs long-term therapy and some patients do not achieve successful outcome. After 1 year of treatment, up to 50% of children are not symptom-free and approximately 30% continue to struggle with constipation beyond the age of puberty.\(^4\)\(^-\)\(^6\) Thus, there seems to be a need to uncover new, more effective interventions in constipated children. The aim of this report is to provide an update on novel and alternative therapies that are already available or have the potential to be helpful options when conventional treatment fails.

Novel drugs

Advancements in the understanding of the gastrointestinal enteric nervous system and epithelial function have led to the development of new classes of drugs for treatment of chronic constipation. These include substances that bind to serotonin receptors and chloride channel activators.

**Tegaserod:** Serotonin plays an important role in regulating gastrointestinal function and 95% of all serotonin in the body is present within the gastrointestinal tract. Tegaserod is a novel selective serotonin receptor agonist that acts at 5-HT4 receptors in the gut wall. It stimulates the peristaltic reflex, enhances intestinal secretions and inhibits visceral sensitivity.\(^7\)\(^,\)\(^8\) It is also a potent prokinetic agent in the upper and lower gastrointestinal tract in both male and female.\(^9\) Tegaserod has proven to be effective in adults with constipation predominant IBS and chronic constipation without IBS symptoms and seems to be beneficial in patients with functional heartburn. Large double blind, placebo controlled trials have demonstrated a significant increase in the
frequency of stools, improvement of stool consistency, and reduction in abdominal symptoms in adults taking tegaserod.\textsuperscript{10-13} Most side effects occurred with similar frequency in both placebo and treatment groups, except for diarrhea which was more common in the tegaserod group. Diarrhea was generally transient and self-limiting, not needing any treatment. Similar results for efficacy and adverse events were found in a study performed in adolescents with constipation predominant IBS.\textsuperscript{14} To date there has only been one abstract reporting the experience on the use of tegaserod in four children with severe chronic constipation.\textsuperscript{15} Preliminary results from a retrospective study conducted at our Center coincide with the adult studies, showing increased bowel movements, decreased abdominal symptoms and minimal side effects in children with a variety of gastrointestinal complaints.

\textbf{Lubiprostone} is an oral bicyclic fatty acid that selectively activates type 2 chloride channels of the gastrointestinal epithelium, resulting in increased fluid secretion. This increase of chloride-rich intestinal fluid softens the stool and accelerates small intestinal and colonic transit.\textsuperscript{16} Lubiprostone was approved by the Food and Drug Administration (FDA) for use in adults with chronic idiopathic constipation in January 2006 after positive results of 2 double-blind, multicenter phase 3 studies in adults with chronic constipation which demonstrated significant improvements in defecation frequency, straining and stool consistency.\textsuperscript{17,18} Overall, lubiprostone appeared to be well tolerated with nausea, diarrhea and headache as most common complaints. No studies of lubiprostone in children have been performed yet.

\textbf{Alvimopan}: Another drug that might have potential to treat constipation is alvimopan. This is a peripherally acting opioid receptor antagonist with a high affinity for \(\mu\)-opioid receptors. This is the site where opioid-binding causes interruption of the coordinated rhythmic contractions of the colon and fluid secretion.\textsuperscript{19} It is unclear whether alvimopan is only effective in opioid-induced constipation or also in subgroups of constipation. Alvimopan has not been approved yet by the FDA and remains a research drug. Enteral \textbf{naloxone} can also improve stool output for pediatric patients who have opioid-induced constipation but carries the risk of introducing withdrawal symptoms which can be harmful to the patient.\textsuperscript{20}

\textbf{Probiotics}

It is becoming increasingly clear that gut bacteria have an important effect on health. The general public is confronted with this notion via the promotion of different yoghurts with a variety of probiotics that are now commercially available and marketed to promote “a healthy gut”. Probiotics are defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (WHO definition). They have traditionally been thought to be useful in the prevention and treatment of various gastrointestinal diseases, including infectious diarrhea,
antibiotic diarrhea, and traveler’s diarrhea. Recently two large human double-blind cross-over randomized studies using 2 different species of probiotics showed improvement in constipation symptoms. One study used one to three portions of Bifidobacterium animalis strain DN-173 010 and reported a significant reduction of colonic transit time (varying from 10-40%) especially in subjects with slow transit (transit time > 40 hours) although no change was observed in the number of stools per week. The other study using Lactobacillus Casei Shirota showed significant improvement in self-reported severity of constipation and stool consistency with a slight but significant increase in stool frequency. In contrast to these latter studies, the only double-blind placebo controlled, randomized study performed in children with constipation studying the effectiveness of Lactobacillus GG as an adjunct to lactulose failed to show any additional benefit.

No probiotic related adverse effects were reported in the studies. The mechanism of action by which probiotics lead to shortening of gut transit time or increase of defecation frequency has not been elucidated yet. Some researchers hypothesize that a product of bacterial origin may decrease sigmoid tone or stimulate colonic motility. Another proposed mechanism is that increasing the concentration of bifidobacteria in the gut may select microflora strains that are resistant to acid conditions, thus modifying the profile of gut microflora and its metabolites, such as short chain fatty acids, and consequently affect transit time. Further studies are needed to assess the clinical efficacy of different species of probiotics in children and to understand the mechanism underlying their effect.

Electrical stimulation

Another approach to treat constipation is electrical stimulation of the bowel, either through sacral nerve stimulation or less invasively with the use of transcutaneous electrical stimulation. Both techniques have been used by urologists for the treatment of detrusor instability and urinary retention in adults and children. Simultaneous improvement of bowel symptoms was often noted by researchers leading to the idea of using electrical stimulation for the treatment of functional bowel disorders. Only a few pilot studies have been published related to sacral nerve stimulation, showing encouraging results in adults with slow transit constipation and those with feeling of incomplete evacuation. Defecation frequency improved together with abdominal and bloating symptoms. Infection of the implant, pain and recurrent cystitis are some of the most common side effects.

Transcutaneous electrical stimulation using interferential current (TESIC) is a non-invasive technique that applies electrical stimuli using surface electrodes over T9-L2. Chase et al. investigated this method in eight children with constipation resistant to chronic treatment and reported increased spontaneous defecation in
6 of the 8 children and reduced fecal incontinence in 7 out of 8 patients. These improvements were maintained for 3 months in up to half of the responders after discontinuation of the electrical stimulation. No adverse reactions were noted during the course of the study. The mechanisms by which sacral nerve stimulation and TESIC exert their effects are still unclear, and long-term, placebo controlled studies are necessary to rule out a placebo effect and determine the ideal treatment duration.

**Acupuncture**
Acupuncture is an ancient Chinese therapy which has been practiced for thousands of years. In recent years, acupuncture has been increasingly accepted throughout the world for the treatment of various conditions although well-designed and controlled studies are still lacking for most diseases to reach definite conclusions. Acupuncture can accelerate the release of opioid peptides in the central nervous system but its effect on constipation and on the opioid activity is not known. One study in children with chronic constipation looked at the effect of acupuncture on symptoms and on basal plasma panopioid level. The study design consisted of a 5 weekly placebo acupuncture sessions followed by 10 weekly true acupuncture sessions. A significant increase of frequency of bowel movement occurred in both boys and girls (1.5 to 4.4/wk vs. 1.4 to 5.6/wk, p<0.01) after treatment. The panopioid activity, which is the ratio of plasma binding to opioid receptors in brain membranes, was lower in the control children and increased only in the children who received the true acupuncture sessions. Out of 27 children who started, 10 children did not complete the study due to poor compliance. In contrast to the study in children, a study performed in adults with chronic constipation did not show any improvement in symptoms.

**Reflexology**
Reflexology is based on the notion that different areas on the hands and feet correspond to glands, organs and other parts of the body and that pressure on those specific areas can have therapeutic effect. The mechanism underlying this treatment is unknown but many believe that the effect is caused by an improvement of blood flow that encourages relaxation and the healing response. The effect of reflexology has also been studied in children with constipation. After six weekly reflexology sessions of 30 minutes, defecation frequencies increased and fecal incontinence decreased. This intervention led to an increase in frequency of bowel movements with only 2% instead of 36% of the study children having less than 1 bowel movement/week during treatment. No side effects were reported but double blind studies with longer follow up are needed to exclude placebo effect and determine its long term outcome.
Abdominal massage for the relief of constipation was once a commonly practiced therapy but its use declined over time. Like other complementary therapies there is now a resurgence of interest in the role that abdominal massage may play in relieving constipation although preliminary studies have been disappointing.\(^{39}\)

**Botulinum toxin**

Anal achalasia, defined as lack of relaxation of the internal anal sphincter (IAS) in the absence of aganglionosis, is an uncommon cause of constipation. The diagnosis is based on the results of anorectal manometry testing showing lack of IAS relaxation in response to rectal distention. Children with IAS achalasia typically have an early onset of symptoms, less fecal incontinence and less withholding behavior.\(^{40}\) By analogy to the treatment of esophageal achalasia, botulinum toxin has been used to treat IAS achalasia. Ciamarra et al described 20 patients with abnormal IAS function who had received a four-quadrant intramuscular injection of Clostridium botulinum toxin. Most children showed an increase in defecation frequency with a variable duration of response, ranging from 1 week to more than 18 months. Four patients eventually underwent a sphincterotomy and eight patients received 2 or 3 more injections with botulinum toxin. Patients experienced no side effects except for two children who had transient rectal pain for a few hours after the procedure. Botulinum toxin seems to have a very specific place in the treatment of chronic constipation caused by IAS achalasia or in children who continue to be symptomatic after surgery for Hirschsprung’s disease.\(^{41}\)

**Surgery**

When symptoms are severe enough to significantly impact the patient’s quality of life, physicians might have to resort to surgery. Especially fecal incontinence which frequently accompanies chronic constipation can have a major impact on social interactions and quality of life of the affected child.\(^{42}\) Until recently, creation of a colostomy and/or performance of a total or partial colectomy were the only available surgical options when non-operative management failed. These surgical interventions were often associated with complications and the colectomy was irreversible. New interventions are now available. A continent appendicostomy or a button cecostomy can be created to allow antegrade administration of enemas. Cecostomy tubes can be safely placed percutaneously by interventional radiology or endoscopy instead of surgery.\(^{43,44}\) Regular colonic lavage results in a significant increase in defecation frequency, reduction of fecal incontinence frequency, and consequently an improvement on quality of life.\(^{43,45}\) Success rates are high in most studies (up to 80%) probably due to careful pre-cecostomy evaluation and patient selection. Older motivated children with a
normal response to colonic stimulants are thought to experience more success than younger children with no response to colonic stimulants.\textsuperscript{46} Potential side effects in children receiving an appendicostomy or cecostomy are stenosis of the cutaneous opening, painful or difficult catheterization, dislodged tubes and leakage around the cecostomy button.\textsuperscript{43,47,48}

\textbf{CONCLUSION}

The treatment of children with chronic constipation can be challenging and may lead to disappointing results for both child/parents and physicians. Thus, it is crucial to be familiar with treatment modalities that go beyond traditional and standard care. Regrettably, most of these therapies have only been trialed in small, mostly adult, patient groups. Large-scale multi-center double-blind randomized controlled trials in children are required to establish their efficacy and safety in the treatment of pediatric constipation.
REFERENCE LIST


