Constipation in infancy and childhood: New insights into pathophysiological aspects and treatment
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SUMMARY

More than 99% of term born infants pass their first stool, meconium, within 48 hours after birth. Preterm born infants, however have a delayed first passage of their stools. Information concerning the total duration of meconium passage is however lacking. In the first part of this thesis duration of passage of meconium as a measure for colonic motility was prospectively compared between preterm and term born infants. Furthermore, characteristics of infant stools such as amount, consistency and colour, were evaluated and served as basis for the development of the ‘Amsterdam’ infant stool form scale.

Constipation, is found in 10.4% of children in both Western and Asian countries, when defined as defecation frequencies below three times per week without evidence for organic disease. In 95% of patients presenting with constipation no organic cause is found. Therefore the second part of this thesis focussed on two specific pathophyisiological mechanisms, the lumbar spinal cord and chloride secretion in the rectum, which might be involved in the development of childhood constipation.

In the last part of the thesis, new treatment regimens as well as existing therapies for constipation were compared in clinical studies.

PART I Stool characteristics and bowel habits

In part I we focused on describing factors responsible for differences in bowel habit aspects, such as stool frequency and consistency, between preterm and term infants. In Chapter 1 meconium passage was compared between preterm and term born infants. This study showed, similar to previous studies, that first passage of meconium was delayed in the preterm born infant. In addition, our new data showed that total duration of meconium stools was also prolonged in preterm infants. We found a mean duration of meconium passage of 8 days in preterm infants compared to 3 days in term born infants. Hence, meconium stools are not only delayed but also prolonged in the premature born infant. A possible explanation might be delayed motility of the gastrointestinal tract in premature born infants. In Chapter 2 we described the development of an infant stool form scale, the “Amsterdam Infant Stool Form Scale”, for infants <24 months of age. This scale can be used as a tool for parents and physicians to describe stool characteristics facilitating diagnosis such as constipation or diarrhoea. The scale describes stool amount, consistency and colour. The use of this scale showed good inter-observer and intra-observer agreement scores. However, future studies are necessary to validate the applicability and validity of this scale for practical and research purposes. In Chapter 3 a cohort of term and preterm born infants were
followed from the first day of life up to the age of 24 months. In the first and second week, breastfed infants had 2.41 more episodes of defecation per week compared to the formula-fed infants. A higher median defecation frequency was only found in week 1 in the term compared to the preterm group. Overall median defecation frequency was 16 (7-30) per week from birth up to the age of 24 months over the total group of participating infants. Based on these findings we conclude that term and preterm born infants have comparable defecation frequency from the second week of life up to the age of 24 months. Additional stool characteristics such as stool colour and consistency were also comparable between both groups during the follow-up period.

**PART II Pathophysiology**

*In part II we focused on elucidating possible underlying pathophysiological mechanisms for functional constipation in children.*

In **Chapter 4** we evaluated chloride secretion in the rectum of children with intractable functional constipation compared to controls. Chloride secretion is a measure for fluid secretion in the colon and plays an important role in water and electrolytes homeostasis. In our study we showed rectal chloride secretion disturbance in children with functional constipation following stimulation with histamine. Whether this defect occurs at the level of the histamine receptor, components of the receptor-linked signal transduction pathway or basolateral Ca$^{2+}$-sensitive K$^+$ channels enhancing the electrical driving force for apical chloride secretion, remains to be explored. In **Chapter 5** we critically evaluated rectal suction biopsies of children with functional constipation, children with Hirschsprung’s disease and controls. It was demonstrated that the rectal muscularis mucosae was thicker in functional constipation compared to Hirschsprung’s disease and controls. No differences were found between characteristics of the muscularis mucosae of controls and children with Hirschsprung’s disease. Interestingly, we found a correlation between duration of functional constipation symptoms and thickness of the muscularis mucosae. The latter finding suggests that the rectal muscularis mucosae hypertrophy might be secondary to constipation symptoms such as rectal faecal impaction. In **Chapter 6** we evaluated the role of spinal cord lesions in childhood constipation. Using magnetic resonance imaging (MRI) we found lumbar sacral spine abnormalities in 3% of children presenting with intractable constipation. Without neurosurgical interventions, all children were successfully treated with laxative and behavioural treatment. Therefore, the relevance of the found lumbo-sacral abnormalities, such as lipomas, remains questionable as all children reached success with conservative treatment only.
PART III Therapy

In part III we evaluated new and compared existing therapeutic regimens for treating childhood functional constipation.

In Chapter 7 two treatment regimens for rectal faecal disimpaction were compared in a randomised controlled manner. Children with constipation and rectal faecal impaction were either randomised for enema therapy or for high doses oral laxatives during 6 consecutive days. We found no statistically different success percentage between both treatment options indicating that rectal enemas (80% success) are not superior to oral laxatives (68% success) for treating rectal faecal impaction. Furthermore fearful behaviour was not more reported in those receiving enemas compared to the group receiving oral laxatives. As expected, oral laxatives were associated with more frequent episodes of faecal incontinence and an increase of watery stools compared to those receiving enema therapy. Given these results, both treatments should be equally considered as first line therapy for treating rectal faecal impaction. Nonetheless, one should take into account the preference, of both the child and/or parents, for prescribing either an oral or rectal intervention. After disimpaction, maintenance therapy with oral laxatives is necessary. In many countries polyethylene glycol (PEG) is the first line maintenance therapy for children with constipation. In Chapter 8, a mixture of probiotics was evaluated in the treatment of childhood constipation. In this uncontrolled study we found that especially children presenting with a defecation frequency <3 times per week had a significant increase in defecation frequency. In addition, all participating children had a decrease in faecal incontinence frequency and episodes of abdominal pain but no difference was found in stool consistency. Since this uncontrolled study showed beneficial effects on symptoms of constipation a randomised placebo controlled trial is justified to evaluate the role of this mixture probiotics in treating functional constipation in children.
DISCUSSION AND FUTURE PERSPECTIVES

To date, little is known about normal bowel habits in the first years of life. The necessity for more prospectively obtained data concerning infants and young children is mandatory, not only to define normal bowel habits but also to recognise abnormal bowel habits such as constipation. Since the Rome III criteria lack clear definitions for constipation in infants, clinical experience is often the reason to start laxative treatment. The results of previous studies evaluating bowel habits in infants, in combination with the use of the Amsterdam infant stool form scale hopefully will lead to a more scientific based treatment of infants with defecation problems. Previously, hard consistency of stools and painful bowel movements were found in the majority of constipated patients younger than 2 years. Accordingly, we showed in chapter 3 of this thesis that hard stools were one of the main reasons to start laxative treatment. Therefore, in addition to defecation frequency, hard stools would also be a good candidate to characterise constipation in infancy. In 2006 the Rome-III committee decided that a defecation frequency fewer than 3 per week is one of the criteria for functional constipation in neonates and toddlers. However we and others clearly showed that the normal defecation frequency in infants < 2 years is 1-2 per day. Therefore we suggest to change the Rome III criterion, defecation frequency, to <1 per day rather than <3 per week for infants 24 months and younger with constipation.

The aetiology of childhood constipation has yet to be further clarified. We therefore evaluated different aetiological aspects of constipation in this thesis. In chapter 4, we found disturbed rectal chloride secretion in children with functional constipation following stimulation with histamine. Whether this defect occurs at the level of the histamine receptor, components of the receptor-linked signal transduction pathway or basolateral Ca^{2+}-sensitive K^+ channels that enhance the electrical driving force for apical chloride secretion, remains to be explored. Yet we only assessed chloride secretion in the rectum rather than in the total colon. In future experiments, assessment of chloride secretion in the different parts of the colon would provide more insight into the importance of disturbed chloride secretion. Lubiprostone is a fatty acid derivative of a metabolite of prostaglandin E1 and acts as a chloride channel activator to increase intestinal fluid secretion and transit. Indeed, several clinical trials showed that chloride secretion stimulation with this chloride channel activator is effective in the treatment of chronic constipation in adults. In children however, such clinical studies have yet to be conducted.

Withholding behaviour is suggested to be the major cause of constipation in children. This conscious contraction of the pelvic floor muscles and consequent faecal stasis in the rectum may cause histological changes in the rectal muscularis mucosae (RMM). Indeed, we found that the RMM was hypertrophied and
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disorganised in children with constipation compared to controls and children with Hirschsprung’s disease. More interestingly, we found a correlation between muscle thickness and duration of symptoms. These findings suggest that muscularis mucosae hypertrophy might be secondary to constipation symptoms such as rectal faecal impaction. To investigate the latter, a study assessing muscle thickness in constipated children before and after therapy (rectal disimpaction and maintenance laxative therapy) is recommended.

Constipation is a common symptom in children with spinal cord lesions. The mechanism by which spinal cord lesions produce constipation is unknown. A retrospective study showed 9% lumbo-sacral abnormalities in children presenting with intractable constipation. More importantly, 88% had symptom relief following neurosurgical treatment. In this thesis we prospectively described a lower prevalence of 3% lumbo-sacral abnormalities in Dutch children with intractable constipation. In healthy adults a comparable prevalence of 1.5-5% spinal lipomas is found. Given the latter and the finding that children from our study reached success with conservative treatment consisting of laxatives, the relevance of the found lumbar sacral abnormalities remains questionable. Therefore we concluded that performing MRI to assess lumbo-sacral spine abnormalities is not required in the standard work-up of children with intractable constipation. The question whether preventive neurosurgery is recommended in lumbo-sacral spine abnormalities, such as lipomas, should be answered by performing large prospective controlled studies in this group of children.

The treatment of children with constipation is mainly based on clinical experience and usually consists of a behavioural strategy with oral and sometimes rectal laxatives. The treatment of chronic constipation in childhood is based on 4 important phases: 1) education, 2) disimpaction, 3) prevention of re-accumulation of faeces and 4) follow up. Up to now we start with the administration of rectal enemas in the majority of children with severe rectal faecal impaction. Our new findings demonstrate however, that rectal enemas and high doses of oral laxatives are both equally effective in removing a rectal faecal mass. As expected, the high dosage of PEG results in a softening of stools and consequently increasing the faecal incontinence frequency. Until the faecaloma has been cleared, soft stool leaks along the rectal faecal mass. In contrast, a rectal enema contains a hypertonic solution which stimulates contraction of the rectosigmoid. These huge contractions result in immediately clearing of the rectal faecal mass, which explains the almost immediate disappearance of faecal incontinence. It is therefore important to inform child and parents that disimpaction with oral laxatives is likely to cause more episodes of faecal incontinence compared to disimpaction with enemas.
For maintenance therapy, despite adequate treatment with laxatives, after one year of laxatives intake, success is achieved in only 62% of children with chronic constipation. Therefore novel therapies, such as probiotics, are studied. Probiotics, defined as live microbial microorganisms, that when administered in adequate amounts confer a health benefit on the host, are now entering mainstream medicine. While an increasing number of potential health benefits are being attributed to probiotic therapies, only a few have been confirmed in well-designed and conducted randomized controlled trials. More importantly, there is a major need for evaluating high-dose probiotic use in healthy infants and children with respect to their safety and tolerance for extended periods. Only one randomised controlled trial is available in the literature evaluating the effect of a probiotic strain in children with constipation. This trial concluded that Lactobacillus GG, as used in this study, was not an effective adjunct to lactulose in treating constipation in children. Just recently a study in healthy infants was conducted using a mixture of probiotics rather than one strain, showing that an infant formula supplemented with a mixture of probiotics, Lactobacillus paracasei ssp. paracasei and Bifidobacterium animalis ssp. Lactis, resulted in more frequent and softer stools compared to infants receiving a formula without the addition of this probiotic mixture. A trial using a probiotics mixture in constipated children was for the first time conducted and described in this thesis. In this uncontrolled trial, we found that a mixture of probiotics, containing lactobacilli and bifidobacteria, decreased abdominal pain as well as faecal incontinence episodes in constipated children. However larger randomised controlled trials are needed to confirm these preliminary data.

Constipation and abdominal pain are the most common gastrointestinal diseases in children. Painful infrequent defecation and involuntary faecal incontinence have great social impact on the child and the family. Nevertheless, well-designed studies are still scarce with respect to pathophysiology, diagnostic work-up, therapy and long term follow-up of children with chronic constipation. To improve the latter, national and international co-operation is needed in order to create consortia aiming to include large numbers of patients.