

The effects and efficacy of (laparoscopic) gastrostomy tube placement in children

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The effects and efficacy of (laparoscopic) gastrostomy tube placement in children

De gevolgen en effectiviteit van (laparoscopische) gastrostomie bij kinderen
(met een samenvatting in het Nederlands)

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Chapter 1

General introduction and outline of thesis

Gastrostomy placement (GP), in which a feeding tube is surgically inserted into the stomach through an incision in the abdominal wall, is a frequently performed operation in children. GP allows enteral nutritional supplementation in children with insufficient oral intake. GP is generally regarded as a safe procedure to provide enteral tube feeding. However, it may have unanticipated effects on gastrointestinal function and is associated with certain complications.^{1,2}

Indications for GP

GP is performed in a wide spectrum of pediatric patients. In a small number of patients indication for GP is application of medications, for example laxatives in chronic obstipation or ketogenic diet in epilepsy (3-5% of patients in our institution). However, in the majority of children indication for GP is malnutrition in children with severe, chronic feeding problems. Main underlying conditions are neurologic impairment, cystic fibrosis, congenital heart or pulmonary disease, metabolic disease and failure to thrive (without a known diagnosis).³⁻⁵

Malnutrition in children

Malnutrition in children is a major threat to pediatric health.^{6,7} A large survey found a prevalence of malnutrition among admitted children in Dutch hospitals of 19%.⁸ In children with known chronic disease, malnutrition was even more common with a prevalence of 51% in academic hospitals and 29% in all hospitals combined.⁸

The consequences of malnutrition are widespread and may be particularly damaging in early life, since malnutrition leads to impaired growth and development.⁹ Decreased muscle strength, including respiratory muscles, results in predisposition to pneumonia.¹⁰ Disturbances in immune function related to malnutrition lead to increased risk of infection.¹⁰ Furthermore, cerebral growth and cognitive development can be impaired.¹¹

For a long period of time, clinicians accepted malnutrition as part of the child's disease. However, with the development of tube feeding, poor nutrition has become an alterable component of chronic diseases in children. For short-term enteral feeding, nasogastric tube feeding is often used. However, this comes with several limitations, including nasal discomfort, risk of pulmonary aspiration and frequent blockage or displacement of the catheter.¹² When chronic tube feeding is required, GP can offer a solution.

History of GP

The operative technique of GP was first described as an open procedure by Martin Stamm in 1894.¹³ This original technique was performed by laparotomy requiring a considerable operative incision, resulting in significant pain and postoperative hospital stay.¹⁴ In 1980, Gauderer *et al.* introduced a less invasive technique involving an endoscopic approach to

place the feeding tube: the percutaneous endoscopic gastrostomy (PEG).¹⁵ Advantages of PEG reflect its less traumatic nature: lower costs, shorter procedure times and higher tolerance for early postoperative feeding.¹⁶ Nowadays, many institutes use PEG as the standard approach in pediatric patients. However, lack of direct visualization of the intraabdominal cavity and subsequent possible injury to surrounding organs is the most imminent disadvantage of this technique.⁴ In 1990, laparoscopic GP was introduced as a safe and effective minimally invasive alternative to PEG.¹⁷ This technique provides a combination of the minimally invasive advantages of the PEG with the safety of direct visualization of the stomach during gastrostomy placement.¹⁴ However, although both minimally invasive techniques are nowadays widely used, still no consensus exists on which type is the preferred procedure in children.

Surgical procedure of laparoscopic GP

An infra-umbilical 6 mm trocar is introduced for the camera. Between the umbilicus and the costal margin, a small incision is made through which a Babcock clamp is introduced to grasp the lateral wall of the corpus under direct laparoscopic view. This part of the stomach is then sutured to the fascia of the abdominal wall with Vicryl sutures in four directions. The stomach is insufflated. With clear laparoscopic view a needle is inserted into the stomach. A peel-away dilator is placed using the Seldinger technique followed by introduction of a gastrostomy catheter. Finally, the balloon of the catheter is inflated with sterile water. Feeding through the gastrostomy, with half of the normal feeding regimen, is initiated on the first postoperative day. Full enteral feeding is administered on the second day after surgery.

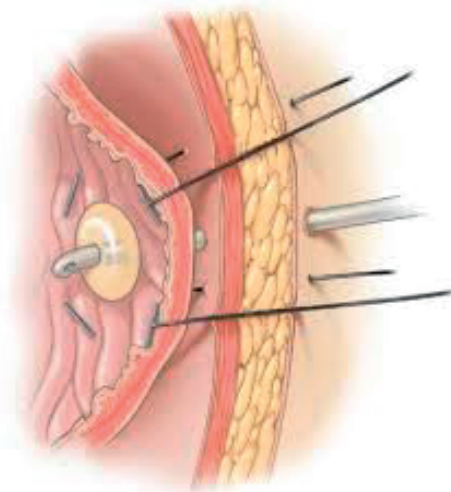


Figure 1. Surgical technique

Efficacy

The most important reason for caregivers to eventually choose for a gastrostomy tube placement is the improvement of nutritional status and quality of life of their child.¹⁸ In the majority of patients, GP is successful because sufficient caloric intake can be provided through the gastrostomy.¹⁹ However, little is known about the long-term efficacy of GP, with either weight and height values or records of long-term postoperative method of feeding.

Adverse events

Perioperative complications during GP are adjacent bowel injury and upper gastrointestinal bleeding. Other major complications are tube migration and intraperitoneal leakage of tube contents because of dehiscence of the gastric wall, which if left untreated leads to sepsis.^{2,20,21}

Furthermore, minor complications associated with gastrostomy tube feeding frequently occur (e.g. gastrostomy site infection or tube dislodgement). Well-designed studies reporting on these complications are limited and reported complication rates vary strongly among different studies.^{1,2}

Gastrointestinal effects of GP

In an estimated 15–25% of patients a gastrostomy fails, characterized by intolerance of feeding with excessive vomiting and/or leakage of gastric contents at the gastrostomy site.²² As an intermediate solution, a gastrojejunostomy tube can be placed as an extension through the gastrostomy into the jejunal part of the small intestine.²² If a gastrojejunostomy does not alleviate symptoms, the gastrostomy can be removed, in which case a laparoscopic jejunostomy placement is performed or patients can be confined to total parenteral nutrition. Based on current evidence, it is unknown which patients are at risk of gastrostomy failure.^{1,23} It is unclear whether gastrostomy failure may be associated with changes in gastric emptying rate and/or the occurrence of gastroesophageal reflux (GER) after GP.

Gastric emptying

Pediatric patients undergoing GP often suffer from profound neurologic impairment.²⁴ Generalized gastrointestinal dysmotility is frequently encountered in these patients.^{25,26} Additionally, the effects of GP itself on gastric emptying are unknown.

Diagnosing gastric emptying: the 13C gastric emptying breath test

99-Tcchnetium scintigraphy was former standard of care for measuring GE in children for a long period of time. In 2005 the 13C gastric emptying breath test (¹³C GEBT) was introduced. The test utilizes a gas isotope ratio mass spectrometer for the measurement of the ratio of 13CO₂ to 12CO₂ in breath samples. In contrast to 99-Tcchnetium scintigraphy, it offers normal values for children of all ages, both genders, and liquid and solid intake.⁴⁶ Additionally, ¹³C GEBT does not involve radiation and is therefore suitable for large pediatric study populations.²⁷

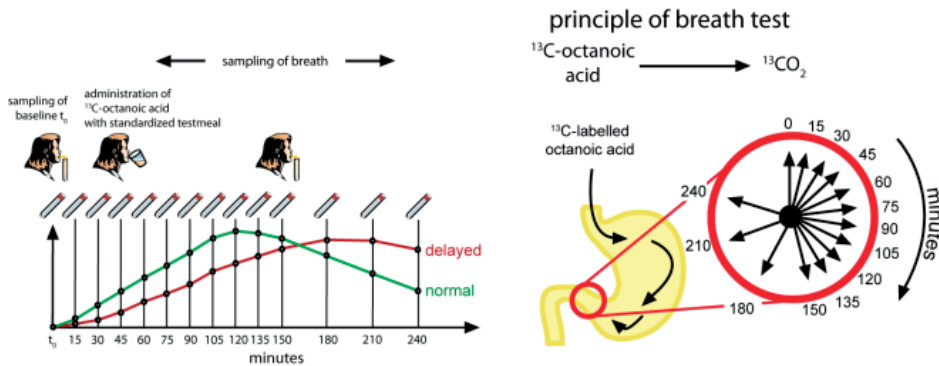


Figure 2. The ^{13}C gastric emptying breath test

Gastroesophageal reflux

A widely discussed possible complication of GP is the development or deterioration of GER. The majority of patients undergoing GP are neurologically impaired and therefore already at high risk of GER.^{3,28} After GP, symptoms of GER are seen in 25–66% of patients.^{5,29,30} In earlier days, a preventive fundoplication was sometimes performed simultaneously with GP in order to prevent future GER.³⁰ Also, some studies advocated the routine use of preoperative 24-h pH monitoring to predict postoperative GER.^{30,31} However, only a few studies have been performed comparing pre- and postoperative values of esophageal pH measurement using 24-hour pH monitoring. While some studies suggest a worsening or development of esophageal acid exposure after operation^{32,33}, other studies show no change or decreased exposure.^{31,34} Consequently, no consensus exists to date.

Diagnosing GER: Questionnaires

For symptom evaluation of GER in children, an age-specific reflux questionnaire has been developed: the infant Gastroesophageal reflux Symptom Questionnaire (GSQ).³⁵ Symptoms assessed are abdominal pain, burping or belching, choking when eating, difficulty swallowing, refusal to eat, vomiting and regurgitation.

Diagnosing GER: 24-hour MII-pH monitoring

Until recently, pH monitoring was considered the gold standard for GER measurement, measuring the frequency and duration of episodes of acidity in the esophagus. The development of multichannel intraluminal impedance (MII) greatly improved accuracy in diagnosing GER.³⁶⁻³⁸ By adding electrical impedance to a pH-monitoring catheter at various levels, this technique detects changes in electrical impedance between two electrodes during the passage of a bolus. The main advantage of MII-pH over traditional pH monitoring is the ability to detect acid, weakly acidic and non-acid reflux episodes and to differentiate between liquid and gas movements within the esophageal lumen.^{36,38,39}

In children, weakly and non-acidic reflux occur more frequently compared to the adult population.⁴⁰

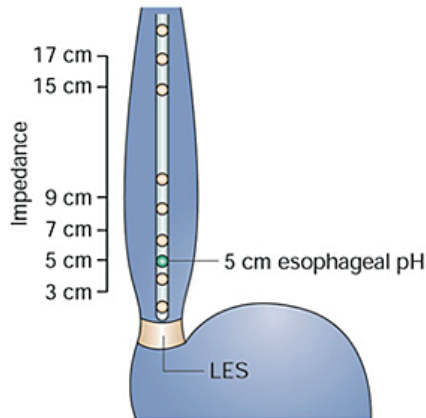


Figure 3. Multichannel intraluminal impedance measurement

Health-related quality of life

The impact of pediatric feeding problems can have a major influence on the child, the parents and family life.⁴¹ GP may possibly not only lead to an improvement in nutritional status, but also to an improvement in other aspects in the lives of these patients. Few studies have considered these broader psychosocial aspects of GP.^{1,19}

Health-related quality of life (HRQoL) is increasingly recognized as an essential component of patient care outcomes.⁴²⁻⁴⁴ Systematic reviews of the literature have shown that the impact of tube feeding on HRQoL has been inadequately studied.^{1,19}

Diagnosing HRQoL: the PedsQL questionnaire

The Pediatric Quality of Life (PedsQL™) 4.0 Generic Core Scale is a reliable and valid tool for proxy-report of HRQoL by caregivers and a parallel self-report for children. It has been used to assess HRQoL in healthy populations, as well as in children with numerous acute and chronic health conditions.⁴³⁻⁴⁵

Aims and outline of this thesis

The work presented in this thesis concerns the effects and efficacy of (laparoscopic) GP in children. The thesis is subdivided into four parts.

I. Percutaneous endoscopic versus laparoscopic gastrostomy placement

In **chapter 2** a systematic review and meta-analysis is presented comparing laparoscopic GP with the traditional percutaneous endoscopic technique. Primary outcomes are success rate, efficacy of feeding, quality of life, gastroesophageal reflux and postoperative complications.

II. Efficacy and adverse events

In **chapter 3** a large retrospective survey is presented analyzing the long-term efficacy and adverse events of GP in a large survey of 300 children. Efficacy of GP is analyzed by method of feeding and weight and length values. Complications and reinterventions are meticulously registered. Pre- and postoperative gastroesophageal reflux (GER) symptoms and the value of routine preoperative 24-hour pH monitoring for predicting postoperative GER symptoms are addressed.

III. Gastrointestinal effects

In this part the effects of GP on gastrointestinal function are analyzed. In **chapter 4** a prospective, longitudinal cohort study is presented analyzing the effect of GP on gastric emptying in children using the ¹³C gastric emptying breath test. We investigate whether delayed gastric emptying is related to postoperative gastrostomy failure.

In **chapter 5** a prospective, longitudinal cohort study is presented analyzing the effect of GP on the occurrence of GER using 24-hour multichannel intraluminal impedance pH monitoring. We aim to identify predictors of the changes in reflux values after operation. The relationship between GER and GE is investigated.

IV. Health-related quality of life

In this part the effect of GP on health-related quality of life (HRQoL) is analyzed.

In **chapter 6** a large retrospective survey is presented analyzing long-term HRQoL in 128 children after GP. HRQoL was evaluated using the validated Pediatric Quality of Life 4.0 Inventory.

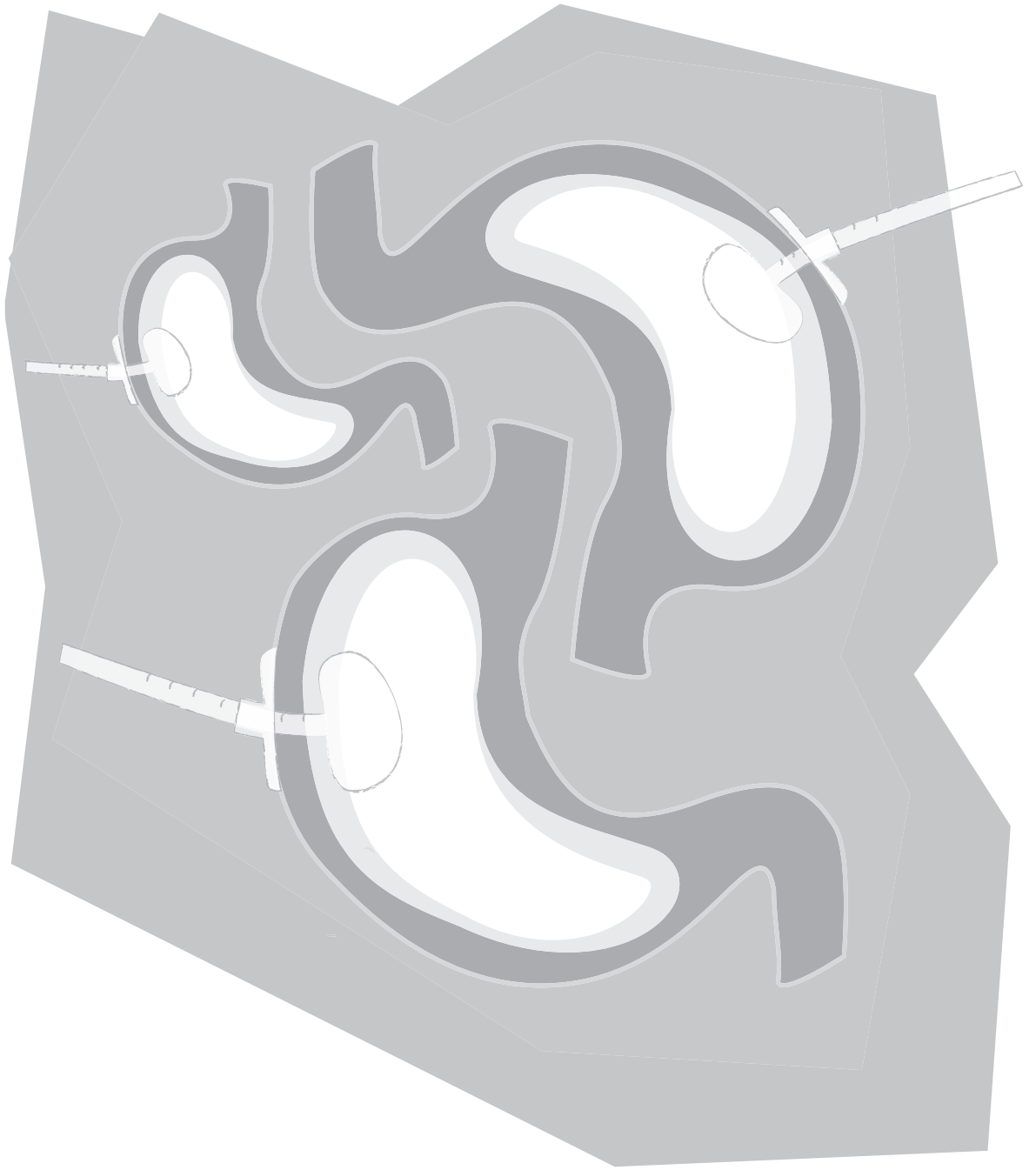
In **chapter 7** a prospective, longitudinal cohort study is presented analyzing the effect of GP on HRQoL comparing pre- and postoperative values.

REFERENCES

1. Samson-Fang L, Butler C, O'Donnell M, AACPDM. Effects of gastrostomy feeding in children with cerebral palsy: An AACPDM evidence report. *Dev Med Child Neurol.* 2003;45(6):415-426.
2. Arnbjornsson E, Larsson LT, Lindhagen T. Complications of laparoscopy-aided gastrostomies in pediatric practice. *J Pediatr Surg.* 1999;34(12):1843-1846.
3. Srinivasan R, Irvine T, Dalzell M. Indications for percutaneous endoscopic gastrostomy and procedure-related outcome. *J Pediatr Gastroenterol Nutr.* 2009;49(5):584-588.
4. Fortunato J CC. Outcomes of percutaneous endoscopic gastrostomy in children. *Curr Gastroenterol Rep* 2011;13(3):293-9.
5. Khattak IU, Kimber C, Kiely EM, Spitz L. Percutaneous endoscopic gastrostomy in paediatric practice: Complications and outcome. *J Pediatr Surg.* 1998;33(1):67-72.
6. Hendricks KM, Duggan C, Gallagher L, et al. Malnutrition in hospitalized pediatric patients. current prevalence. *Arch Pediatr Adolesc Med.* 1995;149(10):1118-1122.
7. Hendrikse W, Reilly J, Weaver L. Malnutrition in a children's hospital. *Clin Nutr.* 1997; 16:13-8.
8. Joosten KFM, Zwart H, Hop WC, et al. Ondervoeding van eenvijfde van kinderen opgenomen in nederlandse ziekenhuizen. *Ned Tijdschr Geneesk.* 2010;154:A1825.
9. Kuperminc MN, Stevenson RD. Growth and nutrition disorders in children with cerebral palsy. *Dev Disabil Res Rev.* 2008;14(2):137-146.
10. Rodriguez L, Cervantes E, Ortiz R. Malnutrition and gastrointestinal and respiratory infections in children: A public health problem. *Int J Environ Res Public Health.* 2011;8(4):1174-1205.
11. Liu J, Raine A, Venables PH, et al. Malnutrition at age 3 years and lower cognitive ability at age 11 years: Independence from psychosocial adversity. *Arch Pediatr Adolesc Med.* 2003;157(6):593-600.
12. Pancorbo-Hidalgo PL, Garcia-Fernandez FP, Ramirez-Perez C. Complications associated with enteral nutrition by nasogastric tube in an internal medicine unit. *J Clin Nurs.* 2001;10(4):482-490.
13. Stamm M. Gastrostomy by a new method. *Med Newsl.* 1984;65.
14. Collins JB,3rd, Georgeson KE, Vicente Y, et al. Comparison of open and laparoscopic gastrostomy and fundoplication in 120 patients. *J Pediatr Surg.* 1995;30(7):1065-70.
15. Gauderer MW, Ponsky JL, Izant RJ. Gastrostomy without laparotomy: A percutaneous endoscopic technique. *J Pediatr Surg.* 1980;15(6):872-875.
16. McCarter TL, Condon SC, Aguilar RC, et al. Randomized prospective trial of early versus delayed feeding after percutaneous endoscopic gastrostomy placement. *Am J Gastroenterol.* 1998;93(3):419-421
17. Georgeson KE. Laparoscopic gastrostomy and fundoplication. *Pediatr Ann.* 1993;22(11):675-677.
18. Martinez-Costa C, Borraz S, Benloch C, et al. Early decision of gastrostomy tube insertion in children with severe developmental disability: A current dilemma. *J Hum Nutr Diet.* 2011;24(2):115-121.
19. Sullivan PB, Juszczak E, Bachlet AM, et al. Gastrostomy tube feeding in children with cerebral palsy: A prospective, longitudinal study. *Dev Med Child Neurol.* 2005;47(2):77-85.
20. Lantz M, Hultin Larsson H, Arnbjornsson E. Literature review comparing laparoscopic and percutaneous endoscopic gastrostomies in a pediatric population. *Int J Pediatr.* 2010;2010:507616.

21. Brewster BD, Weil BR, Ladd AP. Prospective determination of percutaneous endoscopic gastrostomy complication rates in children: Still a safe procedure. *Surgery*. 2012;152(4):714-9.
22. Friedman JN, Ahmed S, Connolly B, et al. Complications associated with image-guided gastrostomy and gastrojejunostomy tubes in children. *Pediatrics*. 2004;114(2):458-461.
23. Naiditch JA, Lautz T, Barsness KA. Postoperative complications in children undergoing gastrostomy tube placement. *J Laparoendosc Adv Surg Tech A*. 2010;20(9):781-785.
24. Srinivasan R, Irvine T, Dalzell M. Indications for percutaneous endoscopic gastrostomy and procedure-related outcome. *J Pediatr Gastroenterol Nutr*. 2009;49(5):584-588.
25. Sullivan PB. Gastrointestinal disorders in children with neurodevelopmental disabilities. *Dev Disabil Res Rev*. 2008;14(2):128-136.
26. Del Giudice E, Staiano A, Capano G, et al. Gastrointestinal manifestations in children with cerebral palsy. *Brain Dev*. 1999;21(5):307-311.
27. Hauser B, De Schepper J, Cavelliers V, et al. Variability of the 13C-octanoic acid breath test for gastric emptying of solids in healthy children. *Aliment Pharmacol Ther*. 2006;23(9):1315-1319.
28. Heine RG, Reddihough DS, Catto-Smith AG. Gastro-oesophageal reflux and feeding problems after gastrostomy in children with severe neurological impairment. *Dev Med Child Neurol*. 1995;37(4):320-329.
29. Mollitt DL, Golladay ES, Seibert JJ. Symptomatic gastroesophageal reflux following gastrostomy in neurologically impaired patients. *Pediatrics*. 1985;75(6):1124-1126.
30. Sulaeman E, Udall JNJ, Brown RF, et al. Gastroesophageal reflux and nissen fundoplication following PEG in children. *J Pediatr Gastroenterol Nutr* 26:269-273. 1998.
31. Wilson GJ, van der Zee DC, Bax NM. Endoscopic gastrostomy placement in the child with gastroesophageal reflux: Is concomitant antireflux surgery indicated? *J Pediatr Surg*. 2006;41(8):1441-1445.
32. Heine RG, Reddihough DS, Catto-Smith AG. Gastro-oesophageal reflux and feeding problems after gastrostomy in children with severe neurological impairment. *Dev Med Child Neurol*. 1995;37(4):320-329.
33. Grunow JE, al-Hafidh A, Tunell WP. Gastroesophageal reflux following percutaneous endoscopic gastrostomy in children. *J Pediatr Surg*. 1989;24(1):42-4.
34. Samuel M, Holmes K. Quantitative and qualitative analysis of gastroesophageal reflux after percutaneous endoscopic gastrostomy. *J Pediatr Surg*. 2002;37(2):256-261.
35. Deal L, Gold BD, Gremse DA, et al. Age-specific questionnaires distinguish GERD symptom frequency and severity in infants and young children: Development and initial validation. *J Pediatr Gastroenterol Nutr*. 2005;41(2):178-185.
36. Skopnik H, Silny J, Heiber O, et al. Gastroesophageal reflux in infants: Evaluation of a new intraluminal impedance technique. *J Pediatr Gastroenterol Nutr*. 1996;23(5):591-598.
37. Noble LJ, Dalzell AM, El-Matary W. The relationship between percutaneous endoscopic gastrostomy and gastro-oesophageal reflux disease in children: A systematic review. *Surg Endosc*. 2012;26(9):2504-2512.
38. Rosen R, Lord C, Nurko S. The sensitivity of multichannel intraluminal impedance and the pH probe in the evaluation of gastroesophageal reflux in children. *Clin Gastroenterol Hepatol*. 2006;4(2):167-172.
39. Van Wijk MP, Benninga MA, Omari TI. Role of the multichannel intraluminal impedance technique in infants and children. *J Pediatr Gastroenterol Nutr*. 2009;48(1):2-12.
40. Rudolph CD, Mazur LJ, Liptak GS, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: Recommendations of the north american

- society for pediatric gastroenterology and nutrition. *J Pediatr Gastroenterol Nutr.* 2001;32 Suppl 2:S1-31.
41. Brotherton AM, Abbott J, Aggett PJ. The impact of percutaneous endoscopic gastrostomy feeding in children; the parental perspective. *Child Care Health Dev.* 2007;33(5):539-546.
 42. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med.* 1993;118(8):622-629.
 43. Varni JW, Limbers CA. The pediatric quality of life inventory: Measuring pediatric health-related quality of life from the perspective of children and their parents. *Pediatr Clin North Am.* 2009;56(4):843-863.
 44. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: Reliability and validity of the pediatric quality of life inventory version 4.0 generic core scales in healthy and patient populations. *Med Care.* 2001;39(8):800-812.
 45. Varni JW, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life?: An analysis of 8,591 children across age subgroups with the PedsQL™ 4.0 generic core scales. *Health Qual Life Outcomes.* 2007;5:1-7525-5-1.



Part I

**Percutaneous versus
laparoscopic gastrostomy**

Chapter 2

Laparoscopic versus percutaneous endoscopic gastrostomy placement in children: results of a systematic review and meta-analysis.

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ABSTRACT

Introduction: Percutaneous endoscopic gastrostomy (PEG) and laparoscopic gastrostomy placement (LGP) are widely used in the pediatric population. The aim of this study was to determine which of both procedures is the most effective and safe method.

Methods: This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses statement. Primary outcomes were success rate, efficacy of feeding, quality of life, gastroesophageal reflux and postoperative complications.

Results: After screening 2347 articles, five retrospective studies were identified comparing 550 PEG to 483 LGP in children. The completion rate was similar for both procedures. PEG was associated with significantly more adjacent bowel injuries ($p = 0.047$), early tube dislodgements ($p = 0.02$) and complications that require reintervention under general anaesthesia ($p < 0.001$). Minor complications were equally frequent after both procedures.

Conclusions: Because of the lack of well-designed studies, we have to be cautious in making definitive conclusions comparing PEG to LGP. To decide which type of GP is best practice in pediatric patients, randomized controlled trials comparing PEG to LGP are highly warranted.

INTRODUCTION

A gastrostomy tube placement is a frequently performed procedure to benefit children with feeding difficulties. The majority of these children have a significant neurological impairment.¹ Less frequent indications are an inadequate caloric intake in children with chronic medical diseases, failure to thrive, oesophageal atresia, dysphagia, short bowel syndrome and malabsorption.²⁻⁴

In 1980, Gauderer *et al.*⁵ introduced percutaneous endoscopic gastrostomy (PEG) as an alternative to the conventional gastrostomy tube placement. Because of its endoscopic approach, this technique is minimally invasive and easy to perform. After the first report, PEG became popular and many authors published on the safety and effectiveness of the procedure.⁶⁻¹⁰ Nowadays, many institutions have used PEG as standard treatment in children.

Pediatric surgeons, later on, introduced laparoscopic gastrostomy placement (LGP) as a safe and effective minimally invasive alternative to PEG.^{11,12} Although both procedures are nowadays widely used, controversy remains on which type is the preferred procedure in the pediatric population.

The main reason for caregivers to eventually choose for a gastrostomy tube placement is an improvement of nutritional status and quality of life (QoL).¹³ Improvement of nutritional status and QoL are depended on the efficacy of enteral feeding and postoperative adverse events.¹⁴ Possible adverse events associated with a gastrostomy are gastroesophageal reflux (GER)¹⁵ and complications requiring reinterventions, such as damage to adjacent organs, hypergranulation at the insertion and gastric content leakage at the gastrostomy site.⁶

None of the studies comparing PEG and LGP were able to conclude which type of approach results in the best nutritional outcome and the lowest risk of developing adverse events.^{16,17} The aim of this study was to determine which type of approach, either PEG or LGP, is best practice in children, through a systematic review and meta-analysis comparing success rates, efficacy of enteral feeding and postoperative adverse events.

METHODS

Search strategy

This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.^{19,20} PubMed (1960–2011),

EMBASE (1980–2011) and the Cochrane Library (December 2012, issue 6) were systematically searched using predefined search terms to identify all articles comparing PEG to LGP. For PubMed, the following search terms were used: (Paediatrics[Mesh] OR child[MeSH] OR child*[tiab] OR infant*[tiab] OR adolescent*[tiab] OR paediatric*[tiab] OR paediatric*[tiab]) AND (Gastrostoma*[tiab] OR 'gastric feeding tube'[tiab] OR gastrostomy[MeSH]). The same search strategy was used in EMBASE (replacing '[Title/Abstract]' with 'ti, ab' and '[MeSH Terms]' with '/exp'). Human, child and adolescent were used as search limits in both databases. Language restrictions and time horizons were not applied.

Study selection criteria

Each article was independently assessed for eligibility using the following predefined criteria:

- Study design: Originally published articles.
- Study population: Infants and children (0–18 years) who underwent gastrostomy placement.
- Intervention: Documented surgical technique.
- Study outcomes: At least one of the outcomes of interest reported below.

Studies were excluded from analysis if the authors performed concomitant antireflux procedures or if primary outcome parameters were not reported. In case of multiple studies reporting on the same study population, only the study with the largest patient population was included.

Outcomes of interest

Primary outcomes of interest were (1) success rates of GP, defined as either completion rate or conversion rate of the procedure, time to first feeding and time to reaching full feedings after operation; (2) efficacy of feeding, defined by the method of feeding and the effects of gastrostomy placement on nutritional status (body mass index, weight-for-height and height-for-age z-scores);¹⁸ (3) QoL, either described or quantified with a validated QoL questionnaire (4) GER, assessed by descriptive symptoms or standardized GER questionnaires and/or 24-hour pH monitoring (with or without multichannel intraluminal impedance) and/or the need for postoperative antireflux surgery; and (5) complications associated with gastrostomy placement (e.g. adjacent bowel injury, early tube dislodgement, intraperitoneal leakage both before and after gastrostomy tube exchange, nonclosure of the gastrostomy after removal of the catheter) and overall rates of complications requiring reintervention under general anaesthesia.

Secondary outcomes of interest were minor complications (e.g. gastric content leakage at the gastrostomy site, infection or hypergranulation of the gastrostomy insertion), operating time, duration of hospital admission and hospital and procedural costs.

Data extraction

Using predefined criteria, titles and abstracts of all retrieved records and subsequently full-text articles were examined for eligibility independently by two authors. A cross-reference check of included articles was performed to identify articles possibly missed by our search strategy. The following data was extracted separately by the same two authors for all studies meeting the inclusion criteria: study population characteristics, study design, surgical method, duration of follow-up, number of participating subjects and events for each of the study outcomes of interest. In the case of discrepancies, a third author was consulted to obtain consensus. Methodological quality and risk of bias were assessed for every included study according to the PRISMA-statement^{19,20} and the Cochrane Collaboration's tool for risk of bias assessment.²¹

Statistical analysis

If more than two studies reported on one of the outcomes of interest, studies were pooled in a meta-analysis. Results were presented as risk ratios (RRs) or weighted mean differences with 95% confidence intervals (CI). The alpha risk was set at 0.05. Data were pooled using the Mantel-Haenszel random-effects meta-analysis model.²² The random-effects model was chosen to take into account suspected heterogeneity caused by differences in study design and patient population, as it generates a more conservative estimate than analysis using the fixed-effects model.²³ Studies were weighted on sample size and the number of events. Trials with zero events in one arm were included in the analysis by adding a continuity correction of 0.5 to all cells in the two-by-two table for that study. Trials with zero events in both arms were excluded from the meta-analysis. Heterogeneity was calculated using Higgins Chi-square test ($p > 0.1$).²⁴ Inconsistency in study effects was quantified by I^2 values ($I^2 > 50\%$).^{24,25} Funnel plots were used to help identify the presence of publication bias or other types of bias.²⁶ All analyses were performed using the Review Manager software provided by The Cochrane Collaboration (version 5.1.7.).

RESULTS

After an extensive literature search, 2347 articles were initially identified. A total of five studies met our in- and exclusion criteria (**Figure 1**).^{16,17,27-29} All studies had a retrospective study design. The five studies reported on a total of 550 PEG and 483 LGP procedures. Gastrostomy placements were performed between 1992 and 2008. Two out of the five studies reported on follow-up time (range 0–135.6 months). All study demographics and surgical techniques are summarized in **Table 1**. A risk of bias overview is given in **Table 2**.

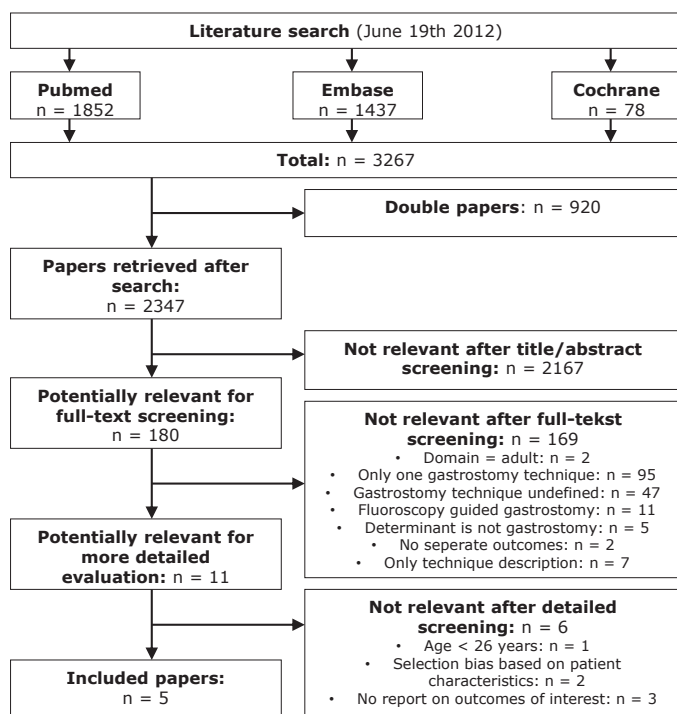


Figure 1. Flowchart of literature search.

Table 1. Studies comparing PEG and LGP in children.

Study (year)	Period	Technique	Number	Mean FU (months)	Neurologic impairment	Male / Female	Age	Surgical technique
Akay 2010	2004	PEG	134	7.4	100%	86/48	7.4	Gauderer technique
	2008	LGP	104					55/49
Fraser 2009	2000	PEG	282	NR	100%	849/685	3	NR
	2008	LGP	270					NR
Zamakhshary 2005	2002	PEG	93	NR	85%	45/48	5	Gauderer technique
	2003	LGP	26					12/14
Conlon 2004	1992	PEG	33	82.8 (0-135.6)	100%	NR	NR	NR
	2002	LGP	75					NR
Lee 2002	1998	PEG	8	NR	100%	NR	NR	NR
	1999	LGP	8					2 sutures through abdominal wall

Legend: FU: Follow-up; NR: Not Recorded; **Techniques:** PEG: Percutaneous endoscopic gastrostomy; LGP: Laparoscopic gastrostomy; **Patients:** NI: Neurologically impaired; **Surgical technique:** * = Modified Rothenberg technique

Table 2 Risk of bias summary

Study (year)	Prospective design	Randomized	Standardization (study protocol)	Adequate report on loss-to-follow-up	Potential other sources of bias
Akay <i>et al.</i> 2010	-	-	-	NA	a, b
Conlon <i>et al.</i> 2004	-	-	-	NA	NR
Fraser <i>et al.</i> 2009	-	-	-	NA	NR
Zamakhshary <i>et al.</i> 2005	-	-	-	NA	c, d
Lee <i>et al.</i> 2002	-	-	-	NA	e

Legend: NR = Not Recorded; NA = Not Applicable (No lost to follow-up).

Standardization: Is the study conducted according to a predefined study protocol?

Loss-to-follow-up: Is there a complete report on loss-to-follow-up?

Potential other bias: a = Gastrostomy with antireflux procedure were excluded; b = Significant difference in age between groups; c = Undefined criteria for patient selection; d = Time horizon determines intervention and e = Only 8 without fundoplication in a total group of 51 patients

Primary outcomes

Only two studies reported on the success rates of the procedure.^{16,17} The completion rates reported by Zamakhshary *et al.*¹⁷ were similar for both groups (98% for PEG vs. 100% for LGP). Akay *et al.*¹⁶ reported on the rate of conversion, which was also similar for both PEG (3.5%) and LGP (4.8%).

Only one study reported data comparing time to enteral feeding.¹⁶ Time to reach first feeding (0.7 vs. 0.8 days) and time to reach full feedings (2.1 vs. 2.3 days) were similar for both PEG and LGP.

None of the studies reported data on the efficacy of enteral feeding, nutritional outcomes or QoL after both procedures.

None of the studies reported on GER symptoms or objective GER measurements. Only one study reported that 17 out of 234 patients (7.3%) who received a gastrostomy required an antireflux procedure to treat severe reflux symptoms. This study did not identify a statistically significant difference between PEG and LGP ($p = 0.425$).¹⁶

Complications were addressed by all five studies. Three studies reported on adjacent bowel injury.^{16,17,27} The risk of damaging adjacent intestine was significantly higher during PEG than during LGP (RR = 5.55, $p = 0.047$); **Figure 2**. There was no adjacent bowel injury in the LGP group. In the PEG group, 2 small bowel perforations and 7 colonic perforations occurred. In one patient, an iatrogenic perforation of the colon was made, and this was identified during the procedure. Consequently, PEG was converted to laparotomy to suture

the colonic perforation. All other perforations were discovered postoperatively after the development of peritonitis, sepsis and/or fecal leakage at the gastrostomy site. All patients with perforations after PEG underwent laparotomy and in one patient a colostomy was needed.

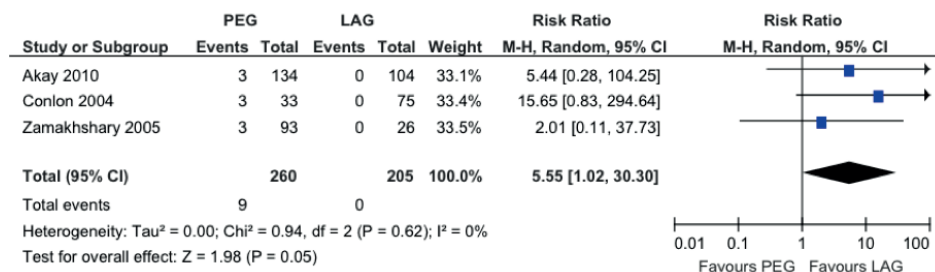


Figure 2: Meta-analysis of adjacent bowel injury after PEG versus LGP.

Legend: Risk ratios are shown in 95% confidence intervals (Mantel–Haenszel random effects model).

Two studies reported data on early tube dislodgement.^{16,27} Patients who underwent PEG had a higher risk of early tube dislodgement (RR = 7.44, $p = 0.02$); **Figure 3**. All patients with early tube dislodgement in the PEG group needed a reintervention under general anaesthesia to replace the gastrostomy tube. The only patient in the LGP group with early tube dislodgement received a new gastrostomy catheter as an outpatient procedure without any form of anaesthesia required.

The time between initial tube placement and first tube change was mentioned in only two studies and varied between 6 and 8 weeks.^{16,17}

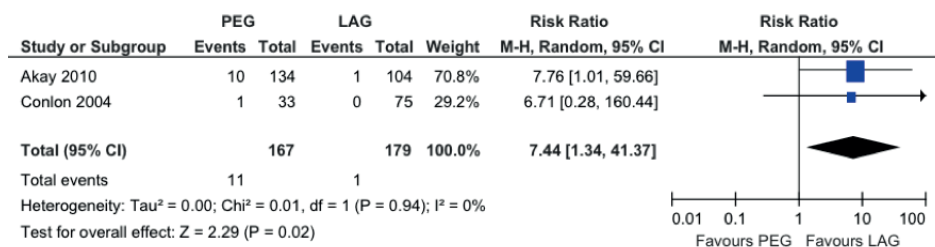


Figure 3: Meta-analysis of early tube dislodgement after PEG versus LGP.

Legend: Risk ratios are shown with 95% confidence intervals (Mantel–Haenszel random effects model).

Only one article reported on intraperitoneal leakage before the first tube change.¹⁷ This study demonstrated similar rates after PEG and LGP (RR = 0.28; $p = 0.36$). After the first tube change, intraperitoneal leakage was reported in two studies.^{16,17} The RR for developing intraperitoneal leakage after tube change after PEG was 3.14 compared to those after LGP. Meta-analysis, did not identify a statistically significant difference ($p = 0.28$).

Two studies reported on cases of non-closure of the gastrostomy site after removal of the catheter requiring surgical closure.^{16,17} The RR of non-closure in children who underwent PEG was 0.94 compared to those who underwent LGP. However, meta-analysis did not identify a statistically significant difference ($p = 0.92$).

Finally, all included articles reported on the number of reinterventions under general anaesthesia. Patients who received a PEG had a RR of 2.79 ($p = 0.0008$) compared to patients who received a LGP; **Figure 4**. The most frequently reported cause for reintervention in patients with PEG was early tube dislodgement. In patients who underwent LGP the most frequently reported causes were stomal complications (e.g. granulation tissue, erosion, ulceration and non-healing skin).¹⁶

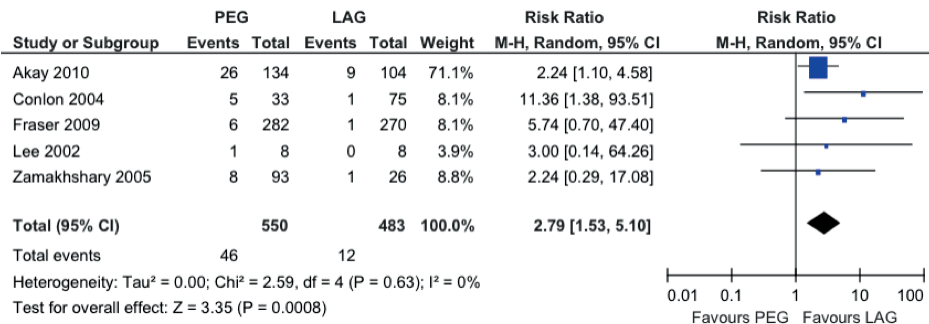


Figure 4. Meta-analysis of all reinterventions requiring general anaesthesia after percutaneous endoscopic gastrostomy versus laparoscopic gastrostomy.

Legend: Risk ratios (RR) are shown with 95% confidence intervals (Mantel-Haenszel random effects model)

To identify possible publication bias, funnel plots were constructed. None of the funnel plots on the primary outcomes showed clear evidence of publication bias, and none of the studies lay outside the 95% CI limits.

Secondary outcomes

Two studies provided data on gastric content leakage at the gastrostomy site.^{27,28} Patients after PEG had an RR of 3.82 compared to those after LGP of developing gastric content leakage. However, this difference was not statistically significant ($p = 0.15$).

Only one article reported on risks of stomal infection requiring treatment.²⁸ This study did not identify a statistically significant difference (0.4% vs.0%, RR=2.87, $p=0.52$).

Two studies reported data on operating time.^{16,17} Akay *et al.*¹⁶ reported significantly shorter operating time for initial gastrostomy in the PEG group ($p = 0.001$). Zamakhshary *et al.*¹⁷ did not identify a difference in operating time (**Table 3**). In this study, routine postoperative

tube change was included in the overall operating time.¹⁷ These were the only two studies^{16,17} describing the specific procedure for the PEG, both using the technique described by Gauderer *et al.*⁵ Three studies described the LGP technique.^{16,17,29} Techniques described were the ‘four tacking sutures technique’¹⁶ and the ‘two anchoring sutures combined with a purse string suture’.¹⁷

Table 3. Operating time

Study (year)	Period	Operating time PEG (min ± SD)	Operating time LGP (min ± SD)	p-value
Akay 2010	2004-2008	25.6 ± 2.4	51.0 ± 2.8	0.001
Zamakhshary 2005	2002-2003	53.7 ± 3.2*	54.4 ± 2.6*	NS

Legend: SD = Standard deviation; * routine postoperative tube change was included in the overall operating time

Only one study compared procedural costs of both initial procedures.²⁹ Lee *et al.* concluded that PEG (1375 USD) resulted in lower procedural costs than LGP (2425 USD), which was explained by the fact that PEG required shorter operating time. However, the costs of the routine second procedure after PEG (to change the gastrostomy catheter to a button) were not included in the total costs.

None of the studies reported exact data comparing length of hospital stay and hospital costs after both PEG and LGP.

After constructing funnel plots, we did not identify evidence indicating publication bias for these secondary outcomes and none of the studies fell outside the 95% CI limits.

DISCUSSION

This systematic review and meta-analysis on PEG versus LGP showed similar success rates in terms of completion or conversion of both procedures, but less major adverse events after LGP.

The most important indication for gastrostomy tube placement in children is to provide successful enteral feeding, as this leads to improvement of nutritional status and QoL. Nevertheless, in this systematic review, we found a lack of studies comparing the efficacy of enteral feeding or effects on QoL between PEG and LGP since none of the studies reported on these outcomes.

Two studies reported on the success of the procedure, showing a completion rate of almost 100% after both PEG and LGP¹⁷ and a conversion rate of only 3–5%.¹⁶ This is similar to recently published prospective studies on gastrostomy placement.^{6,30,31} The learning curve or level of training of the physician may be of influence on the surgical outcome, however, none of the studies reported details on surgical and/or endoscopic training.

Many publications reported on the effects of gastrostomy placement on GER.^{15,32-34} However, the exact correlation between gastrostomy and the development of GER remains unclear.³⁵ In this systematic review, none of the comparative studies between PEG and LGP reported on GER. Perhaps this lack of published data is caused by the fact that the majority of children requiring long-term enteral tube feeding are neurologically impaired and that specifically in this group evaluation of GER is difficult. GER symptoms are often atypical, and may be disguised by other gastrointestinal problems. Furthermore, normal values of 24-hour pH monitoring are not available for children and adolescents, with the exception of early infancy.³⁶⁻³⁸

Meta-analysis of serious adverse events identified that patients undergoing PEG had a higher risk (RR 5.55) of injury to the adjacent bowel. PEG is placed from an endoscopic intragastric view, in which a needle is introduced through the abdominal wall without a view on the position of adjacent organs. Major complications, such as adjacent bowel injuries and catheter misplacement are therefore more common after PEG compared to LGP.³⁹⁻⁴² Furthermore, when such complications occurred, endoscopic view could not provide early detection, which may have led to more morbidity.

Zamakhshary *et al.*¹⁷ reported transcolonic tube placement in three children. In all three children, this was diagnosed postoperatively after faecal drainage via the gastrostomy. In none of the patients undergoing LGP adjacent bowel injuries occurred. The laparoscopic approach is possibly safer as it provides a clear intra-abdominal view, thereby preventing adjacent bowel injury.^{43,44} Moreover, laparoscopic surgery can detect and immediately correct major complications during this primary procedure.

The meta-analysis of early tube dislodgement identified a seven times higher risk of dislodgement for children undergoing PEG than for those undergoing LGP. Tube dislodgement can lead to serious complications, such as intraperitoneal leakage of gastric content, mainly when the gastrostomy was recently performed.⁴⁵ During a LGP, the stomach is always firmly attached to the abdominal wall with several sutures. If early tube dislodgement occurs, replacement with a new catheter during an outpatient procedure can be performed with a negligible chance of developing adverse events.¹⁶ Patients with a PEG initially only have the gastrostomy tube itself to attach the stomach to the abdominal

wall. Therefore, during the first week after initial placement, the tract may not be stable enough to safely exchange or reinsert the gastrostomy tube. To underline this, in this meta-analysis, we found that all patients with early tube dislodgement after PEG required reintervention under general anaesthesia.¹⁶

A new technique with a modified T-fastener PEG has been developed to secure a more tight connection and, therefore, it is thought to provide less morbidity in the case of dislodgement.⁴⁶ Unfortunately, the authors did not separately report on using T-fasteners during PEG. Therefore, comparison of PEG with T-fasteners to PEG without T-fasteners is not possible.

In 8.4% (2.1–19.4%) of children who underwent PEG a reintervention requiring general anaesthesia was needed, while in children who underwent LGP only 2.5% (0–8.6%) returned to the operating theatre for reintervention. Meta-analysis confirmed a significant difference (RR = 2.79; $p = 0.0008$) in favour of LGP. General anaesthesia can be hazardous, especially in patients with cardiac and/or pulmonary anomalies. Therefore, specifically in these patients, LGP could be preferred in order to minimize the risk of multiple (routine) procedures under general anaesthesia.⁴⁷

Minor complications may play an important role in QoL of patients and their caretakers, especially in children with a long-term indication for gastrostomy use.⁴⁸ Stomal infection and leakage of gastric contents at the gastrostomy site were similar after PEG and LGP. Nevertheless, infection rates are difficult to compare because studies do not specify if these infections were confirmed by positive wound cultures or if patients were treated with antibiotics. Hypergranulation is a complication that occurs very frequently after gastrostomy placement. It can cause bleeding and leakage from the gastrostomy site and can be reason for reoperation and thus have a major influence on QoL.⁶ However, no studies could be identified comparing the incidence of postoperative hypergranulation between PEG and LGP.

PEG is thought to be a faster procedure than LGP; in this study, only two studies compared operating time, of which only one found a significant difference in favour of PEG.¹⁶ In the study by Zamakhshary *et al.*¹⁷ PEG and LGP required similar operating time, possibly because the operating time of the second routine procedure (to change the gastrostomy tube to a button) was included in the operating time of PEG. In PEG, even though the initial placement required less operating time, most patients required a second procedure under anaesthesia for routine tube change. In patients who underwent LGP, this routine tube change could be performed in the outpatient clinic.^{17,49} The surgeon should take the need for a second procedure under general anaesthesia after PEG into consideration.

Finally, a number of issues still need to be considered regarding the conclusions of this systematic review and meta-analysis. First, all of the included studies in this review were retrospective in design, which resulted in limited access to study outcomes and susceptibility to various forms of bias (mainly confounding and selection bias). Second, patient populations, in terms of comorbidities (e.g., neurologically impaired children, children with congenital cardiac disease and children with cystic fibrosis), were heterogeneous, and studies did not report separate data outcomes comparing specific patient groups. In the meta-analysis, however, none of the outcomes demonstrated excessive heterogeneity. To further take possible effects of heterogeneity between studies into account, we used the random-effects model for meta-analysis, as it generates a more conservative estimate than an analysis using the fixed-effects model.²³ Third, none of the studies used standardized questionnaires or investigation techniques to objectively assess outcomes of efficacy. And finally, patients were operated between 1992 and 2008 and not all authors described their specific surgical techniques in detail. Gastrostomy placement techniques, especially PEG, have changed over the years.^{46,50,51} However, the main concept of each procedure (e.g. endoscopic versus laparoscopic view) remained similar.

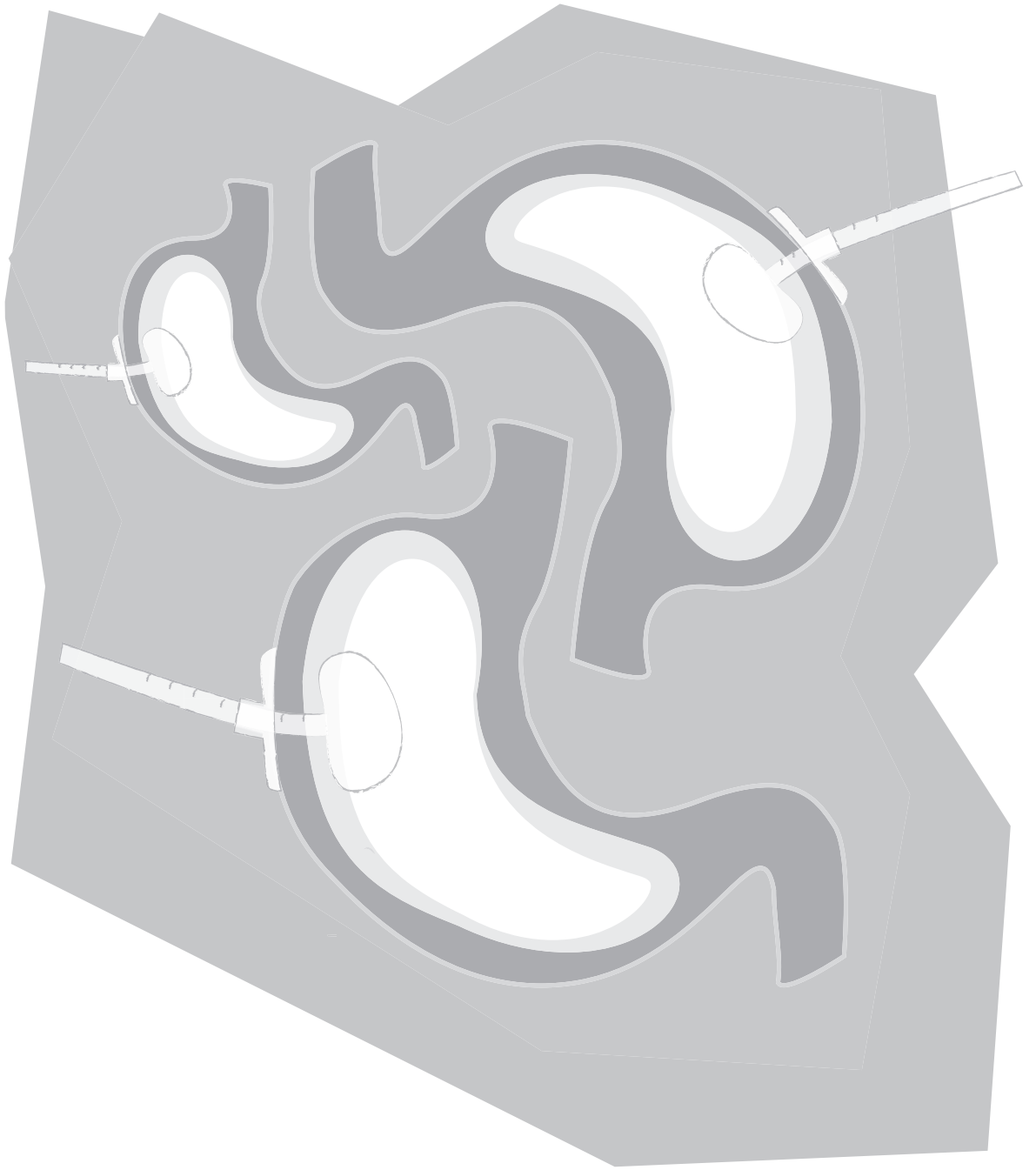
This systematic review and meta-analysis demonstrate that current literature lacks well-designed studies comparing outcomes such as efficacy of feeding, QoL and GER and, therefore, we have to be cautious in making definitive conclusions. However, there are retrospective studies available that compare PEG versus LGP and report actual data suitable for systematic review and meta-analysis. These studies cannot simply be discarded and are needed to provide patients, caregivers and referring physicians with evidence-based information on both procedures. Systematic review and meta-analysis of these data show that the success rates in terms of completion of the procedure were similar for PEG and LGP. However, LGP was associated with significantly less serious adverse events, namely adjacent bowel injury and early tube dislodgement, and a lower rate of reinterventions that required general anaesthesia. Naturally, to make a more informed decision on which procedure of gastrostomy placement is best practice in children, randomized controlled trials comparing LGP to PEG are highly warranted.

REFERENCES

1. Srinivasan R, Irvine T, Dalzell M. Indications for percutaneous endoscopic gastrostomy and procedure-related outcome. *J Pediatr Gastroenterol Nutr* 2009;49:584-8.
2. Fortunato JE, Troy AL, Cuffari C, et al. Outcome after percutaneous endoscopic gastrostomy in children and young adults. *J Pediatr Gastroenterol Nutr* 2010;50:390-3.
3. Khattak IU, Kimber C, Kiely EM, et al. Percutaneous endoscopic gastrostomy in paediatric practice: complications and outcome. *J Pediatr Surg* 1998;33:67-72.
4. Tomicic JT, Luks FI, Shalon L, et al. Laparoscopic gastrostomy in infants and children. *Eur J Pediatr Surg* 2002;12:107-10.
5. Gauderer MW, Ponsky JL, Izant RJ Jr. Gastrostomy without laparotomy: a percutaneous endoscopic technique. *J Pediatr Surg* 1980;15:872-5.
6. Brewster BD, Weil BR, Ladd AP. Prospective determination of percutaneous endoscopic gastrostomy complication rates in children: still a safe procedure. *Surgery* 2012;152:714-9.
7. Minar P, Garland J, Martinez A, et al. Safety of percutaneous endoscopic gastrostomy in medically complicated infants. *J Pediatr Gastroenterol Nutr* 2011;53:293-5.
8. Saitua F, Acuna R, Herrera P. Percutaneous endoscopic gastrostomy: the technique of choice? *J Pediatr Surg* 2003;38:1512-5.
9. Terry NE, Boswell WC, Carney DE, et al. Percutaneous endoscopic gastrostomy with T-bar fixation in children and infants. *Surg Endosc* 2008;22:167-70.
10. Van der Merwe WG, Brown RA, Ireland JD, et al. Percutaneous endoscopic gastrostomy in children--a 5-year experience. *S Afr Med J* 2003;93:781-5.
11. Georgeson KE. Laparoscopic gastrostomy and fundoplication. *Pediatr Ann* 1993;22:675-7.
12. Rothenberg SS. Laparoscopic anti-reflux procedures and gastrostomy tubes in infants and children. *Int Surg* 1994;79:328-31.
13. Martinez-Costa C, Borraz S, Benlloch C, et al. Early decision of gastrostomy tube insertion in children with severe developmental disability: a current dilemma. *J Hum Nutr Diet* 2011;24:115-21.
14. Schmitt F, Caldari D, Corradini N, et al. Tolerance and efficacy of preventive gastrostomy feeding in pediatric oncology. *Pediatr Blood Cancer* 2012;59:874-80.
15. Lintula H, Kokki H, Juvonen P, et al. Severe gastro-oesophageal reflux necessitating fundoplication after percutaneous endoscopic and open gastrostomy in children. *Langenbecks Arch Surg* 2012.
16. Akay B, Capizzani TR, Lee AM, et al. Gastrostomy tube placement in infants and children: is there a preferred technique? *J Pediatr Surg* 2010;45:1147-52.
17. Zamakhshary M, Jamal M, Blair GK, et al. Laparoscopic vs percutaneous endoscopic gastrostomy tube insertion: a new pediatric gold standard? *J Pediatr Surg* 2005;40:859-62.
18. WMO Global Database on Child Growth and Malnutrition. 2013.
19. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
20. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
21. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* JohnWiley: Chichester, 2008.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.

23. DeMets DL. Methods for combining randomized clinical trials: strengths and limitations. *Stat Med* 1987;6:341-50.
24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.
25. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
26. Egger M, Davey SG, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
27. Conlon SJ, Janik TA, Janik JS, et al. Gastrostomy revision: incidence and indications. *J Pediatr Surg* 2004;39:1390-5.
28. Fraser JD, Ponsky TA, Aguayo P, et al. Short-term natural history of the standard approaches for gastrostomy tube placement in the pediatric patient. *J Laparoendosc Adv Surg Tech A* 2009;19:567-9.
29. Lee H, Jones A, Vasudevan S, et al. Evaluation of Laparoscopy-Assisted Percutaneous Gastrostomy Tube Placement in Children. *Pediatric Endosurgery & Innovative Techniques* 2002;6:29-32.
30. Mahant S, Friedman JN, Connolly B, et al. Tube feeding and quality of life in children with severe neurological impairment. *Arch Dis Child* 2009;94:668-73.
31. Plantin I, Arnbjornsson E, Larsson LT. No increase in gastroesophageal reflux after laparoscopic gastrostomy in children. *Pediatr Surg Int* 2006;22:581-4.
32. Heine RG, Reddihough DS, Catto-Smith AG. Gastro-oesophageal reflux and feeding problems after gastrostomy in children with severe neurological impairment. *Dev Med Child Neurol* 1995;37:320-9.
33. Thomson M, Rao P, Rawat D, et al. Percutaneous endoscopic gastrostomy and gastro-oesophageal reflux in neurologically impaired children. *World J Gastroenterol* 2011;17:191-6.
34. Wilson GJ, Van der Zee DC, Bax NM. Endoscopic gastrostomy placement in the child with gastroesophageal reflux: is concomitant antireflux surgery indicated? *J Pediatr Surg* 2006;41:1441-5.
35. Noble LJ, Dalzell AM, El-Matary W. The relationship between percutaneous endoscopic gastrostomy and gastro-oesophageal reflux disease in children: a systematic review. *Surg Endosc* 2012;26:2504-12.
36. Hassall E. Decisions in diagnosing and managing chronic gastroesophageal reflux disease in children. *J Pediatr* 2005;146:S3-12.
37. Vandenplas Y, Sacre-Smits L. Continuous 24-hour esophageal pH monitoring in 285 asymptomatic infants 0-15 months old. *J Pediatr Gastroenterol Nutr* 1987;6:220-4.
38. Vandenplas Y, Goyvaerts H, Helven R, et al. Gastroesophageal reflux, as measured by 24-hour pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. *Pediatrics* 1991;88:834-40.
39. Chen Y, Ni YH, Lai HS. Gastrocolocutaneous fistula in a child with congenital short bowel syndrome: a rare complication of percutaneous endoscopic gastrostomy. *J Formos Med Assoc* 2004;103:306-10.
40. Patwardhan N, McHugh K, Drake D, et al. Gastroenteric fistula complicating percutaneous endoscopic gastrostomy. *J Pediatr Surg* 2004;39:561-4.
41. Segal D, Michaud L, Guimber D, et al. Late-onset complications of percutaneous endoscopic gastrostomy in children. *J Pediatr Gastroenterol Nutr* 2001;33:495-500.

42. Stefan MM, Holcomb GW III, Ross AJ III. Cologastric fistula as a complication of percutaneous endoscopic gastrostomy. *JPEN J Parenter Enteral Nutr* 1989;13:554-6.
43. Humphrey GM, Najmaldin A. Laparoscopic gastrostomy in children. *Pediatr Surg Int* 1997;12:501-4.
44. Jones VS, La Hei ER, Shun A. Laparoscopic gastrostomy: the preferred method of gastrostomy in children. *Pediatr Surg Int* 2007;23:1085-9.
45. Rosenberger LH, Newhook T, Schirmer B, et al. Late accidental dislodgement of a percutaneous endoscopic gastrostomy tube: an underestimated burden on patients and the health care system. *Surg Endosc* 2011;25:3307-11.
46. Timratana P, El-Hayek K, Shimizu H, et al. Percutaneous endoscopic gastrostomy (PEG) with T-fasteners obviates the need for emergent replacement after early tube dislodgement. *Surg Endosc* 2012;26:3541-7.
47. Gillory LA, Megison ML, Harmon CM, et al. Laparoscopic surgery in children with congenital heart disease. *J Pediatr Surg* 2012;47:1084-8.
48. Brotherton AM, Abbott J, Aggett PJ. The impact of percutaneous endoscopic gastrostomy feeding in children; the parental perspective. *Child Care Health Dev* 2007;33:539-46.
49. Wragg RC, Salminen H, Pacht M, et al. Gastrostomy insertion in the 21st century: PEG or laparoscopic? Report from a large single-centre series. *Pediatr Surg Int* 2012;28:443-8.
50. Deitel M, Bendago M, Spratt EH, et al. Percutaneous endoscopic gastrostomy by the "pull" and "introducer" methods. *Can J Surg* 1988;31:102-4.
51. Gauderer MW. Percutaneous endoscopic gastrostomy-20 years later: a historical perspective. *J Pediatr Surg* 2001;36:217-9.



Part II

Efficacy and adverse events

Chapter 3

Efficacy and adverse events of laparoscopic gastrostomy placement in children: results of a large cohort study.

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ABSTRACT

Introduction: A gastrostomy placement is frequently performed in pediatric patients who require long-term enteral tube feeding. However, data on efficacy, perioperative complications and postoperative gastroesophageal reflux (GER) after laparoscopic gastrostomy placement (LGP) is limited. The aim of this study is to evaluate long-term efficacy and adverse events after LGP in a large cohort and determine whether routine preoperative 24-hour pH monitoring should be used to predict postoperative GER.

Methods: A retrospective observational cohort study was performed including 300 patients (75% neurologically impaired) that underwent LGP.

Results: After a median follow-up of 2.63 years, feeding was successful in 95.9 % of patients. Weight-for-height z-scores significantly increased ($p < 0.0005$). Major complications were seen in only 6 patients (2.0%), but minor complications occurred frequently (73.6%). The overall incidence of GER remained unchanged after LGP. Sensitivity and specificity of preoperative pH monitoring were 17.5 and 76.9%, respectively.

Conclusion: LGP in pediatric patients leads to successful feeding in 96% of patients and serious adverse events are rare. However, the minor complication rate is high. Overall incidence of GER does not increase after LGP. Preoperative 24-hour pH monitoring is not a reliable tool to predict postoperative GER. This invasive investigation technique should therefore not be routinely performed.

INTRODUCTION

The placement of a gastrostomy tube is an established treatment to benefit pediatric patients with feeding difficulties by providing enteral feeding directly into the stomach. The majority of these children have significant neurological impairment.¹ Less frequently occurring indications for gastrostomy placement are inadequate caloric intake in children with chronic medical conditions, failure to thrive, dysphagia, short bowel syndrome and malabsorption.²⁻⁴ Currently, gastrostomy placements are performed by minimally invasive techniques, either via laparoscopic gastrostomy placement (LGP) or percutaneous endoscopic gastrostomy (PEG). The LGP is the standard approach in our institution, mainly because it is thought that LGP obviates the need for a second procedure using general anesthesia to change the gastrostomy catheter to a button, has a lower complication rate and is associated with shorter hospital stay when compared to PEG.^{5,6}

The two most important aims when placing a gastrostomy are improvement of nutritional status^{7,8} and improvement of quality of life (QoL). Achievement of these aims is determined by efficacy of enteral feeding via the gastrostomy and possible adverse events associated with the gastrostomy.^{8,9}

Frequently reported adverse events associated with gastrostomy placement are hypergranulation tissue, leakage of gastric contents at the gastrostomy site and gastrostomy site infections.^{10,11} These complications are not life-threatening. However, they are associated with increased health care utilization.¹¹ Well-designed studies reporting on these adverse events are limited, as is shown in a recent systematic review.⁹

Another possible adverse effect of a gastrostomy placement is gastroesophageal reflux (GER). GER symptoms are seen in 25–66% of patients after gastrostomy placement.^{3,12,13} Until now, only a few studies have performed 24-hour pH monitoring to obtain objective data on GER before and after gastrostomy placement. Some authors advocate the routine use of preoperative 24-hour pH monitoring to predict postoperative GER.^{13,14} In these studies, patients with preoperative pathological reflux more often developed postoperative GER symptoms after LGP requiring antireflux surgery (ARS). However, two other studies using 24-hour pH monitoring both before and after gastrostomy placement could not identify an increase in pathological GER.^{15,16}

These conflicting study results about the efficacy of gastrostomy feeding and possible adverse events after LGP may hinder the decision-making process for caregivers and physicians. The aim of this study is, therefore, to evaluate the long-term efficacy and

adverse events of LGP in a large cohort and to determine the value of routine preoperative 24-hour pH monitoring for predicting postoperative GER after LGP.

METHODS

Study design

A retrospective observational cohort study including all patients that underwent LGP in the Wilhelmina Children's Hospital between January 2004 and December 2011 was performed. The medical records of all patients were retrospectively reviewed using the electronic medical record. All clinical data were recorded in a database.

Table 1. Patient characteristics

Demographics	
Total number of patients	300
	Median (years)
Age at time of operation	2.66 (IQR 1.28 – 7.44)
Follow-up time	2.63 (IQR 1.07 – 4.77)
	n (%)
Male gender	158 (52.7%)
Neurologically impaired development	225 (75.0%)

Legend: IQR: interquartile range, N: number

Participants

A total of 300 patients with a median age of 2.66 years (IQR 1.28–7.44) were included. Patient characteristics are described in **Table 1**. Indications for LGP were inability to obtain adequate nutrition (99.0%) orally, which resulted in failure to thrive and/or growth retardation.

In 3 patients (1.0%) indication for LGP was to guarantee a safe route for administering medication. The main underlying diseases were neurological disorders (75.0%) and cystic fibrosis (9.7%). Neurological impairment was mostly manifested as psychomotor retardation, epilepsy, microcephaly, spasticity, visual impairment and/or hypotonia.

Surgical procedure

All children underwent LGP under general anesthesia. All procedures were performed or supervised by an experienced pediatric surgeon. An infra-umbilical 6 mm trocar was introduced for the camera. Between the umbilicus and the costal margin, a small incision was made through which a Babcock clamp was introduced to grasp the lateral wall of the corpus under direct laparoscopic view. This part of the stomach was then sutured to

the fascia of the abdominal wall with Vicryl sutures in four directions. The stomach was insufflated by the anesthesiologist. With clear laparoscopic view a needle was inserted into the stomach. A peel-away dilator was placed using the Seldinger technique followed by introduction of a gastrostomy catheter. Finally, the balloon of the catheter was inflated with sterile water. Feeding through the gastrostomy, with half of the normal feeding regimen, was initiated on the first postoperative day. Full enteral feeding was administered on the second day after surgery.

Clinical assessment

The following outcomes were evaluated:

- (1) efficacy of LGP, determined by conversion rate, successful feeding and nutritional status and
- (2) adverse events, defined as major and minor complications, reinterventions and GER symptoms.

Successful feeding; defined as:

- (1) complete enteral feeding via gastrostomy;
- (2) return to complete oral feeding after gastrostomy feeding or
- (3) a combination of oral feeding and feeding via gastrostomy.

Alternative methods of feeding, such as feeding via a nasogastric tube, nasoduodenal tube, gastrojejunostomy, jejunostomy or total parenteral nutrition, were considered unsuccessful.

Nutritional status

Weight and height measurements were converted to weight-for-height and height-for-age z-scores based on the Netherlands Organization for Applied Scientific Research (TNO) growth standards.¹⁷ Z-scores allow comparison of an individual's weight or height, adjusting for age and sex relative to a reference population, expressed in standard deviations from the reference mean.

Adverse events

Major complications were defined as procedure-related death, postoperative dehiscence of the stomach wall, intraoperative or postoperative bleedings, perforation of adjacent organs, acute intestinal obstruction, volvulus and omental herniation. Minor complications were defined as hypergranulation at the gastrostomy insertion requiring treatment with silver nitrate or surgical excision, ectopic gastric mucosa requiring surgical excision, stomal infection requiring treatment with antibiotics or antifungal medication, gastric content leakage at the gastrostomy insertion, dislodgement or obstruction of the catheter requiring

intervention, nonclosure of the gastrostomy after removal of the catheter, catheter size mismatch, gastroparesis, dumping syndrome and the development of crustaceous eczema at the gastrostomy site.

Reinterventions

Reinterventions were defined as all adverse events after LGP requiring an intervention in the operating theater or at the radiology department.

Gastroesophageal reflux

GER symptoms before and after LGP and the need for concomitant and/or secondary ARS were evaluated. Symptoms of persistent vomiting, frequent aspiration, heartburn and/or regurgitation were used to define GER. Preoperative 24-hour pH monitoring was performed in 189 of all 300 patients. In 180 patients (60%) preoperative 24-hour pH monitoring was successful and in 9 patients it had failed due to incorrect placement of the pH probe or dislocation of the probe during the measurement.

Pathological acid exposure was defined as total acid exposure time >6%, or >3% in upright and >9% in supine body position.^{18,19}

Statistical analysis

The efficacy of LGP was analyzed using only the patients who underwent LGP for long-term enteral feeding. Patients who underwent LGP for administering medication were only included in the analysis of adverse events.

Continuous variables, when parametric, were expressed as mean \pm standard error of the mean (SEM). Non-parametric variables were expressed as median, with interquartile ranges (IQR). For continuous parametric outcomes a paired sample T-test was performed. Non-parametric continuous outcomes were analyzed using the Wilcoxon signed-rank test. The Chi squared test was used to analyze dichotomous outcomes. In case dichotomous outcomes were repeated measures the McNemar's test was used. Additionally, sensitivity and specificity of preoperative 24-hour pH monitoring on predicting postoperative GER symptoms were calculated. Differences with a $p < 0.05$ were considered statistically significant. All analyses were performed using SPSS statistical package (IBM, USA).

RESULTS

Median follow-up time was 2.63 years (IQR 1.07–4.77). During follow-up, twenty-six patients (8.7%) had died of causes unrelated to LGP. Causes of death were deterioration

of neurologic disease (n=23), cystic fibrosis (n=2) and advanced cardiac disease (n=1). The majority of patients (83%) received full feedings within 2 days of LGP. Median postoperative hospital stay was 3 days (IQR 2–4.75).

Efficacy

In almost all patients, LGP could be completed laparoscopically. In only 2 patients (0.7 %) conversion to a minilaparotomy was required. In the first patient, intra-abdominal view was compromised by air insufflation of the stomach during intubation. In the second patient, with a history of bronchopulmonary dysplasia and congenital heart disease, abdominal CO₂ insufflation led to respiratory problems. To maintain optimal ventilation, the surgeon converted to minilaparotomy.

A summary of feeding methods during long-term follow-up of all available patients is shown in **Figure 1**. In 34 patients, the method of feeding could not be evaluated because patients had died during follow-up (n=26), the gastrostomy was only used for administering medication (n=3), or no specific feeding method was recorded in the patient records (n=5). Therefore, 266 patients were available for evaluation of feeding method, which was successful in 255 (95.9%) of these patients.

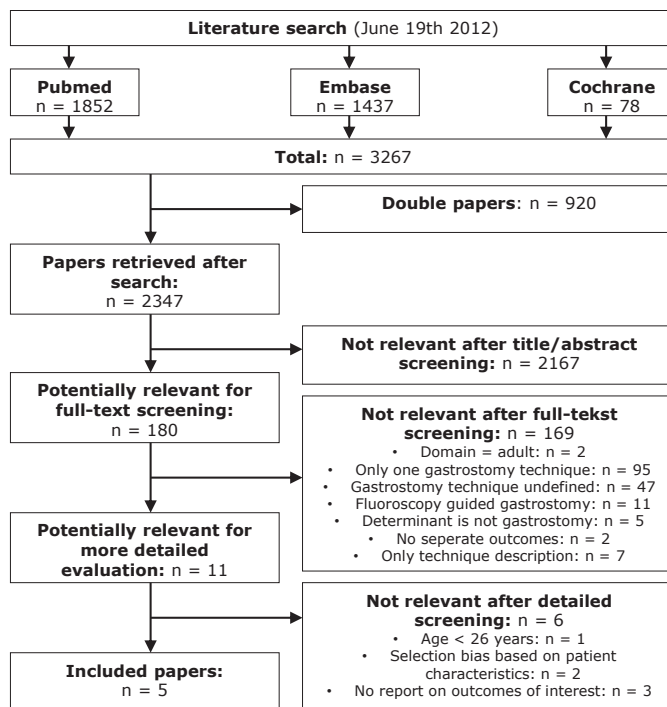


Figure 1. Flowchart of patient inclusion

Legend: TPN = total parenteral nutrition

The gastrostomy was removed in 34 patients (12.8%). In 30 of these patients removal was possible because of reintroduction of full oral feeds. In the remaining 4 patients, however, removal was due to gastrostomy-related complications, predominantly leakage around the insertion site.

In total, 42 (15.8%) patients were able to return to complete oral feeds. In 12 of these patients the gastrostomy was not yet removed. Reasons to keep the gastrostomy were administering of medication, gastric draining or the anticipation of feeding problems in the near future. Patients with normal neurological development returned to complete oral feeding more frequently compared to patients with neurological impairment ($p < 0.0005$). Eleven patients (4.1%) could not be fed via the gastrostomy and required an alternative method of feeding during follow-up. These were gastrojejunal feeding, nasoduodenal tube feeding, jejunal feeding after laparoscopic jejunostomy placement and total parenteral nutrition. Indications for an alternative route of feeding were excessive leakage of gastric contents at the gastrostomy site or persistent vomiting. In three out of five patients with persistent vomiting a gastric function test was performed which showed severely delayed gastric emptying.

At follow-up, 213 (71.0%) patients still received enteral feeding through their gastrostomy. The majority of these patients ($n = 127$; 42.3%) received successful bolus feeding. In 82 of the patients (27.3%) partial or complete continuous drip-feeding was administered. For four patients, no specific feeding schedule was registered in the patient records.

Nutritional status improved after LGP, as weight-for-height z-scores significantly increased ($p < 0.0005$), although height-for-age z-scores remained similar ($p = 0.70$; **Table 2**).

Table 2. Nutritional status

	Preoperative	At follow-up	p-value
Mean weight-for-height z-score (95% CI)	-0.98 (-1.29 – -0.67)	-0.26 (-0.50 – -0.02)	<0.005
Mean height-for-age z-score (95% CI)	-1.62 (-2.01 – -1.22)	-1.54 (-1.80 – -1.29)	0.70

Legend: 95% CI: 95% confidence interval

Adverse events

A total number of 414 minor and major complications were identified (**Table 3**). Only 70 patients (26.3%) were completely free of complications. In 25 patients (8.3%) more than three minor complications occurred during follow-up.

Six patients (2%) had a major complication. In four patients a dehiscence of the gastric wall occurred after operation. These patients presented with peritonitis and sepsis and required

one or more reinterventions to re-attach the stomach to the abdominal wall and drain intraabdominal abscesses. All four patients fully recovered. In one patient (0.3%) injury to the gastric artery led to an intraoperative bleeding. This was successfully treated with diathermic coagulation. One patient (0.3%) had a postoperative herniation of omentum through the gastrostomy site, requiring a revision of the gastrostomy. Perforation of adjacent organs, acute intestinal obstruction and volvulus did not occur.

In 221 patients (73.7%), 408 minor complications occurred. In 38 patients (12.7%) minor complications required reintervention. Hypergranulation (n=132; 44%) was the most frequently encountered minor complication. The initial treatment was application of silver nitrate. In three patients a surgical debridement was eventually needed. Gastrostomy site infection occurred in 74 patients (24.7%), requiring oral antibiotics in 66 patients and antifungal medication in 8 patients. Leakage of gastric contents via the gastrostomy site occurred in 72 patients (24.0%). This was treated conservatively in the majority of patients (n = 60; 20.0%) by temporarily removing the tube or button in order to reduce the diameter of the gastrostomy or by temporary reduction of enteral feeding. Seven patients (2.3%) temporarily received a nasoduodenal catheter to bypass the stomach and consequently reduce the gastrostomy opening. In five patients (1.7%) the gastrostomy had to be revised in the operating theater. No correlation was found between leakage of gastric contents and the time when feeding via the gastrostomy tube was initiated. Dislodgement of the gastrostomy tube occurred in 63 patients (21.0%), requiring reintroduction. In one patient, a fausse route was created during reintroduction. This patient required laparoscopic closure of the fausse route and repositioning of the gastrostomy.

Table 3. Complications of LGP (n=300).

Complications	n (%)
Major complications	6 (2.0%)
Postoperative dehiscence of stomach wall	4 (1.3%)
Intraoperative bleeding	1 (0.3%)
Postoperative omental herniation	1 (0.3%)
Minor complications*	408
Number of patients with minor complications	221 (73.7%)
Hypergranulation	132 (44.0%)
Stomal infection	74 (24.7%)
Leakage at gastrostomy site	72 (24.0%)
Dislodgement of the catheter	63 (21.0%)
Obstruction of the catheter	19 (6.3%)
Non- closure of gastrostomy site	12 (4.0%)
Ectopic gastric mucosa	8 (2.7%)
Others	28 (9.3%)

Legend: * Some patients experienced multiple minor complications

A total number of 48 reinterventions was required to treat major and minor complications. Forty-one of these interventions were performed in the operating theater under general anesthesia. The other 7 reinterventions were nasojejun tube placements under fluoroscopic guidance.

Gastroesophageal reflux

Before LGP, 167 of 289 patients (57.8%) had GER symptoms. After LGP the number of patients with GER was similar (147 of 271 patients; 54.2%; $p=0.824$; **Table 4**). Patients without preoperative GER developed postoperative GER symptoms in 34.2%. In 28.2% of patients with preoperative GER, reflux symptoms dissolved after operation.

Table 4. Pre- and postoperative GER symptoms (n=297).

	Postoperative GER	No postoperative GER	Postoperatively NR	Total
Preoperative GER	107	42	18	167
No preoperative GER	39	75	8	122
<i>Preoperatively NR</i>	1	7		
Total	147	124		297

Legend: NR: Not recorded in patient records

In 180 patients (60%) preoperative 24-hour pH monitoring was completed successfully. Preoperative pathological reflux was present in 32 (17.8%) of these 180. When comparing these patients with a preoperative pathological pH study to the patients with a normal pH study (82.2%), the number of patients with postoperative GER symptoms was evenly distributed ($p=0.384$). The sensitivity and specificity of preoperative pH monitoring in predicting postoperative reflux symptoms were 17.5% and 76.9% respectively (**Table 5**).

Table 5. Results of preoperative 24-hour pH-monitoring compared to postoperative reflux complaints

Preoperative pH monitoring	Postoperative reflux complaints	No postoperative reflux complaints	NR	
Pathological reflux	17	15	5	SENS=17.5%
Normal pH monitoring	80	50	13	SPEC=76.9%
<i>Failed</i>	5	4	0	
<i>No measurement</i>	45	55	11	

Legend: NR: Not recorded in patient records; Sens: sensitivity; Spec: specificity

Concomitant ARS at the time of LGP was not performed. ARS secondary to LGP was performed in two (0.7%) patients. In both patients the indication for ARS was refractory GER. Only one of these patients underwent 24-hour pH monitoring prior to ARS. However,

pathological reflux was not identified and both patients were operated based on GER symptoms.

DISCUSSION

This large, retrospective long-term cohort study showed that LGP in children is a successful treatment in providing a long-lasting and safe route for enteral tube feeding. No study has yet reported on the long-term efficacy of pediatric gastrostomy placement.

In nearly all patients (99.3%), gastrostomy placement could be completed laparoscopically. Also, LGP enabled successful enteral feeding in nearly all pediatric patients (95.9%). Nearly 16% of patients successfully returned to complete oral feeding. Most of these patients were neurologically normal. In only 4.1% of patients an alternative feeding route was necessary to safeguard sufficient enteral feeding after initial LGP. Most of these patients were neurologically impaired and suffered from significant comorbidity consisting of congenital cardiac deformities and/or respiratory problems.

Nutritional status improved significantly after LGP, as weight-for-height z-scores significantly increased compared to the normal mean score of the reference population. Height-for-age z-scores remained similar. However, previous studies on catch-up growth in children recovering from malnutrition showed that weight-for-height measures are the only reliable indicator for improvement of nutritional status, as height-for-age measures are generally more delayed during catch-up growth.^{20,21} Moreover, the majority of included patients is neurologically impaired and these children have impaired linear growth regardless of improvement of nutritional status.⁷

Evaluation of adverse events showed us that LGP is a safe procedure, since the number of major complications is low (2.0%). This is in line with previous publications.^{22,23} Procedure-related mortality did not occur, although the overall mortality rate was reasonably high (8.7%). Mortality was due to deterioration of the underlying disorder in all cases.

In contrast to the low rate of major complications, minor complications occurred in the majority of patients after LGP. Minor complications often result in increased health care utilization because of significant discomfort and frequent hospital consultations¹¹ and should therefore be taken into account when LGP is considered in a pediatric patient. Hypergranulation, gastrostomy site infection, leakage of gastric contents and gastrostomy tube dislodgement were the most frequently reported minor complications. Most studies on adverse events after gastrostomies in pediatric patients reported lower rates of

gastrostomy site infections and higher rates of hypergranulation and leakage.^{11,23,24} These differences in complication rates may be caused by a difference in placement technique, as almost all studies reported solely on PEG in children.^{11,23,24} Also, study design may play a role. Our cohort study, as well as many earlier studies, was performed retrospectively. This may result in missing data and therefore could influence results. All patients in our cohort study, however, were followed very closely by intensive and easily accessible postoperative consultations with the specialized stoma care nurses in our institution. This resulted in very detailed reports on all postoperative events reported in our study.

Several studies have reported on the association between LGP and the incidence of postoperative GER. However, results from these studies are contradictory and well-designed studies with adequate power are lacking.^{14, 16, 25, 26} Our cohort study showed that LGP was not associated with an overall increase in GER incidence, as the number of patients with postoperative GER symptoms remained similar ($p=0.824$) to the number of patients with preoperative GER symptoms. However, assessment of GER in children undergoing LGP is challenging, especially because the vast majority of children requiring long-term enteral feeding are neurologically impaired. In these neurologically impaired patients evaluation of GER symptoms is especially difficult, since symptoms are vague and often disguised by other gastrointestinal problems.²⁷ In addition, data on GER symptoms were collected retrospectively from patient records. In case of missing information on GER symptoms, patients were excluded from analysis.

Assessment of GER was also performed by preoperative 24-hour pH monitoring. In our study, specificity of 24-hour pH monitoring to predict postoperative GER symptoms was relatively high (76.9%), but sensitivity was very low (17.5 %). This means that when the pH metry before LGP shows pathologic reflux, the patient is likely to develop postoperative GER after LGP. However, the vast majority of patients that developed postoperative GER symptoms after LGP were not diagnosed on preoperative pH monitoring. There are missing data on results of the pH monitoring since it was performed in only 60.0% of patients. GER symptoms were reported slightly more frequently in the group of patients with a preoperative pH metry compared to the group without preoperative pH metry (57.2% vs. 45.0%). However, specificity and sensitivity of the pH metry are not dependent on the prevalence of preoperative GER symptoms.

The interpretation of 24-hour pH monitoring results is restricted by certain limitations. First, no normal values are available for patients over 16 months of age.^{28,29} Secondly, pH monitoring only registers the acidic reflux episodes. Non-acidic reflux episodes, which occur more frequently in children compared to the adult population, are not registered. Therefore, because of the low sensitivity and the limitations associated with 24-hour pH

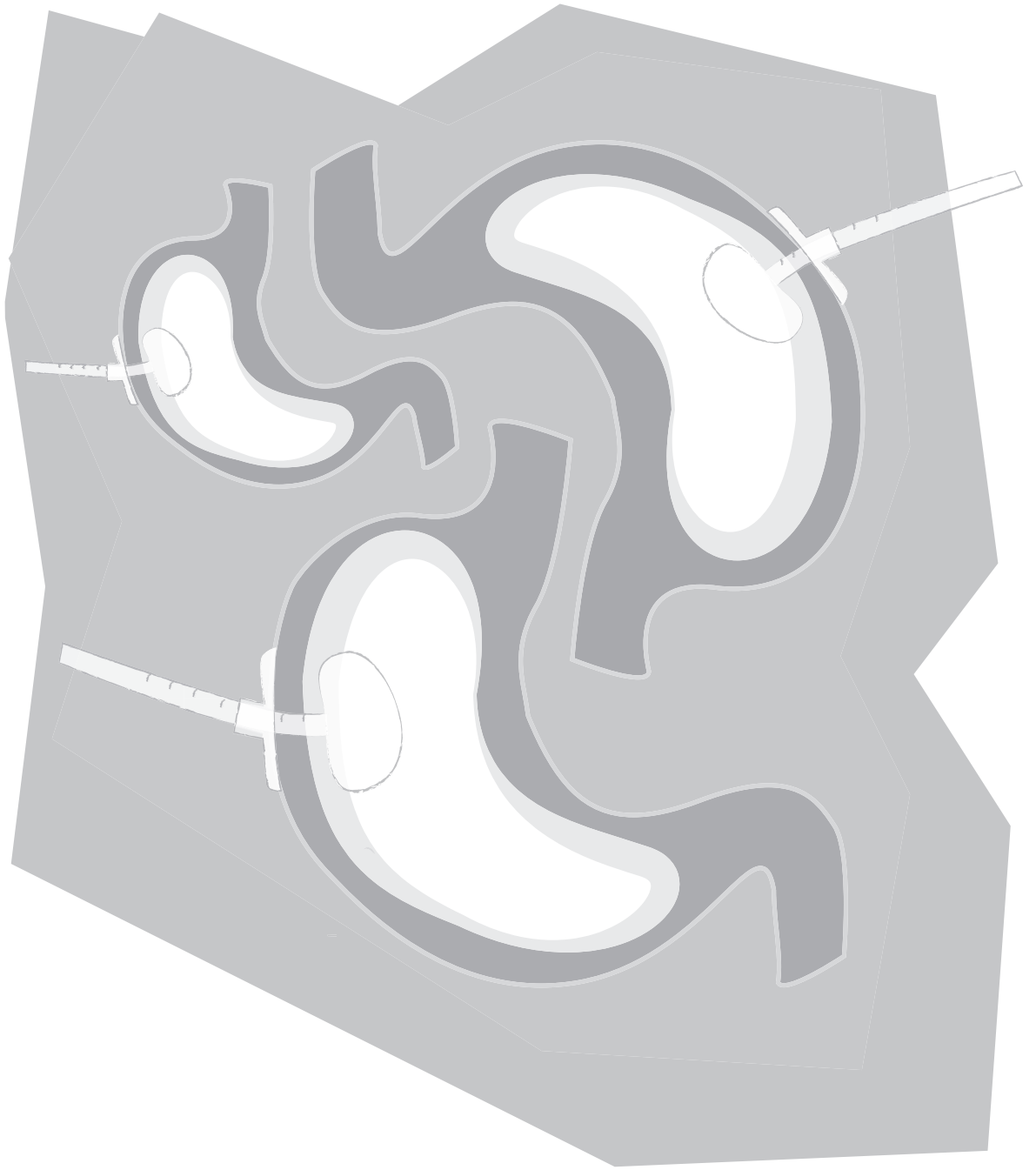
monitoring, routine pH monitoring before LGP does not result in a reliable prognostic value for the development of postoperative GER.

In conclusion, LGP in children enables successful feeding in 96% of patients and is associated with a low risk of developing serious adverse events. Our study reveals a high rate of minor complications. In contrast to previous studies, the incidence of GER symptoms did not increase after LGP. Preoperative 24-hour pH monitoring is not a reliable tool to accurately predict postoperative GER and therefore should not be routinely performed.

REFERENCES

1. Srinivasan R, Irvine T, Dalzell M. Indications for PEG and procedure-related outcome. *J Pediatr Gastroenterol* 2009; 49:584–588.
2. Fortunato JE, Troy AL, Cuffari C, et al. Outcome after PEG in children and young adults. *J Pediatr Gastroenterol Nutr* 2010; 50:390–393
3. Khattak IU, Kimber C, Kiely EM, et al. PEG in paediatric practice: complications and outcome. *J Pediatr Surg* 1998; 33:67–72
4. Tomicic JT, Luks FI, Shalon L, et al. LAG in infants and children. *Eur J Pediatr Surg* 2002; 12:107–110
5. Wragg RC, Salminen H, Pachtl M, et al. Gastrostomy insertion in the 21st century: PEG or laparoscopic? Report from a large single-centre series. *Pediatr Surg Int* 2012; 28:443–448
6. Zamakhshary M, Jamal M, Blair GK, et al. Laparoscopic vs PEG tube insertion: a new pediatric gold standard? *J Pediatr Surg* 2005; 40:859–862
7. Rempel GR, Colwell SO, Nelson RP. Growth in children with cerebral palsy fed via gastrostomy. *Pediatrics* 1998; 82:857–862
8. Corwin DS, Isaacs JS, Georgeson KE, et al. Weight and length increases in children after gastrostomy placement. *J Am Diet Assoc* 1996; 96:874–879
9. Samson-Fang L, Butler C, O'Donnell M. Effects of gastrostomy feeding in children with cerebral palsy: an AACPDM evidence report. *Dev Med Child Neurol* 2003; 45:415–426
10. Brewster BD, Weil BR, Ladd AP. Prospective determination of PEG complication rates in children: still a safe procedure. *Surgery* 2012; 152:714–719
11. Crosby J, Duerksen D. A retrospective survey of tube-related complications in patients receiving long-term home enteral nutrition. *Dig Dis Sci* 2005; 50:1712–1717
12. Mollitt DL, Golladay ES, Seibert JJ. Symptomatic gastroesophageal reflux following gastrostomy in neurologically impaired patients. *Pediatrics* 1985; 75:1124–1126
13. Sulaeman E, Udall JN Jr, Brown RF, et al. Gastroesophageal reflux and Nissen fundoplication following PEG in children. *J Pediatr Gastroenterol Nutr* 1998; 26:269–273
14. Wilson GJ, van der Zee DC, Bax. Endoscopic gastrostomy placement in the child with gastroesophageal reflux: is concomitant ARS indicated? *J Pediatr Surg* 2006; 41:1441–1445
15. Razeghi S, Lang T, Behrens R. Influence of PEG on gastroesophageal reflux: a prospective study in 68 children. *J Pediatr Gastroenterol Nutr* 2002; 35:27–30
16. Thomson M, Rao P, Rawat D, et al. PEG and gastroesophageal reflux in neurologically impaired children. *World J Gastroenterol* 2011; 17:191–196
17. TNO Groeicalculator voor de vijfde landelijke Groeistudie. 2013. Ref Type: Internet Communication
18. Richter JE, Bradley LA, DeMeester T, et al. Normal 24-h ambulatory esophageal pH values. Influence of study center, pH electrode, age and gender. *Dig Dis Sci* 1992; 37:849–856
19. Smout AJ, Breedijk M, van der Zouw C, et al. Physiological gastroesophageal reflux and esophageal motor activity studied with a new system for 24-h recording and automated analysis. *Dig Dis Sci* 1989; 34:372–378
20. Kang A, Zamora SA, Scott RB, et al. Catch-up growth in children treated with home enteral nutrition. *Pediatrics* 1998; 102:951–955
21. Walker SP, Golden MH. Growth in of children recovering from severe malnutrition. *Eur J Clin Nutr* 1988; 42:395–404

22. Lantz M, Hultin LH, Arnbjornsson. Literature review comparing laparoscopic and percutaneous endoscopic gastrostomies in a pediatric population. *Int J Pediatr* 2010;507616
23. Arnbjornsson E, Larsson LT, Lindhagen T. Complications of laparoscopy-aided gastrostomies in pediatric practice. *J Pediatr Surg* 1999; 34:1843–1846
24. Thorne SE, Radford MJ. A comparative longitudinal study of gastrostomy devices in children. *West J Nurs Res* 1998; 20:145–159.
25. Lintula H, Juvonen P, Hamynen I, et al. Severe gastro-oesophageal reflux necessitating fundoplication after percutaneous endoscopic and open gastrostomy in children. *Langenbecks Arch Surg* 2013; 398:703–707
26. Noble LJ, Dalzell AM, El-Matary W. The relationship between PEG and gastro-oesophageal reflux disease in children: a systematic review. *Surg Endosc* 2012; 26:2504–2512
27. Hassall E. Decisions in diagnosing and managing chronic gastroesophageal reflux disease in children. *J Pediatr* 2005; 146:S3–S12
28. Vandenplas Y, Sacre-Smits L. Continuous 24-h esophageal pH monitoring in 285 asymptomatic infants 0–15 months old. *J Pediatr Gastroenterol Nutr* 1987; 6:220–224
29. Vandenplas Y, Goyvaerts H, Helven R, et al. Gastroesophageal reflux, as measured by 24-h pH monitoring, in 509 healthy infants screened for risk of sudden infant death syndrome. *Pediatrics* 1991; 88:834–840



Part III

Gastrointestinal effects

Chapter 4

The effect of gastrostomy placement on gastric function in children: a prospective cohort study

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ABSTRACT

Introduction: A gastrostomy placement is frequently performed in pediatric patients who require long-term enteral tube feeding. Unfortunately, postoperative complications such as leakage, feeding intolerance and gastroesophageal reflux frequently occur. These complications may be due to postoperative gastric dysmotility. Our aim was to evaluate the effect of gastrostomy placement on gastric emptying in children.

Methods: A prospective study was performed including 50 children undergoing laparoscopic gastrostomy. Before and 3 months after gastrostomy, assessment was performed using the ¹³C-octanoic acid breath test, 24-hour pH monitoring and reflux symptom questionnaires.

Results: Gastric half-emptying time significantly increased from the 57th percentile to the 79th percentile after gastrostomy ($p < 0.001$). Fifty percent of patients with normal preoperative gastric emptying develop delayed gastric emptying (DGE) (>95th percentile) after gastrostomy ($p = 0.01$). Most patients ($\geq 75\%$) with leakage and/or feeding intolerance after gastrostomy had DGE after operation. A decrease in gastric emptying was associated with an increase in esophageal acid exposure time ($r = 0.375$; $p < 0.001$).

Conclusion: Gastrostomy placement in children causes a significant delay in gastric emptying. Postoperative DGE was associated with gastroesophageal reflux and was found in most patients with postoperative leakage and feeding intolerance. These negative physiologic effects should be taken into account when considering gastrostomy placement in children.

INTRODUCTION

A gastrostomy placement (GP) is frequently performed in pediatric patients to provide prolonged enteral tube feeding. Although GP is a common procedure, the effects of the operation on gastric motility are unknown. In the majority of patients a GP is successful, because in time, sufficient caloric intake can be provided through the gastrostomy.^{1,2} However, in an estimated 15-25% of patients a gastrostomy fails, leading to intolerance of feeding and leakage at the gastrostomy site.^{3,4} It is unclear whether these complications may be due to delayed gastric emptying (DGE) after operation. Based on current evidence, it is unknown which patients are at risk of gastrostomy failure.^{5,6}

Another, widely discussed, complication of GP is the development or deterioration of gastroesophageal reflux (GER). GER is frequently associated with abnormal gastric motility.^{7,8} DGE after GP may therefore be associated with postoperative GER. Hence, the importance of investigating GP and gastric motility.

In adults, the effect of a GP on gastric emptying (GE) has been investigated by two studies, detecting no significant changes in GE after operation.^{9,10} In children, only one retrospective study on GP and GE was performed, including 26 patients.¹¹ This study was conducted with the ¹³C-octanoic acid gastric emptying breath test (¹³CGEBT) and detected no significant changes in GE after operation. This ¹³CGEBT is a reliable, safe and non-invasive diagnostic method for GE in children.¹² No prospective studies on GE before and after GP in children have been performed to date.

The aim of this study was to evaluate the effect of GP on GE in children using the non-invasive ¹³CGEBT and to identify parameters predictive of gastrostomy failure.

METHODS

Study design

A prospective, longitudinal cohort study including 50 pediatric patients was performed. Between May 2012 and April 2014, all children (aged 0-18 years) referred for GP to the Wilhelmina Children's Hospital were considered for participation. Patients with a history of gastric surgery, with structural abnormalities of the stomach or who were unable to undergo the assessment tests were excluded from the study.

Ethical approval and trial registration

The study was registered at the Dutch trial register before the start of the study (NTR3314, 29-02-2012). Ethical approval was obtained from the University Medical Center Utrecht Ethics Committee. Prior to initiating any study procedure, informed consent was obtained from the patients' parents and the patients themselves (when 12 years or older and not neurologically impaired (NI)).

Surgical procedure

In all children a laparoscopic GP was performed under general anaesthesia. All procedures were performed or supervised by an experienced pediatric surgeon. An infra-umbilical 6 mm trocar was introduced for the camera. The position of the gastrostomy was determined between the umbilicus and the costal margin. A small incision was made introducing a Babcock clamp to grasp the ventral wall of the gastric corpus under direct laparoscopic view. After pulling up the corpus, the gastric wall was sutured to the fascia of the abdominal wall with four interrupted sutures. After insufflation of the stomach, a needle was inserted through the gastric wall. Using the Seldinger technique, a peel-away dilator was placed followed by insertion of a gastrostomy tube. The gastrostomy balloon was inflated with sterile water.

On the first day after surgery, enteral feeding through the gastrostomy was initiated with half of the normal feeding regimen. On the second postoperative day, full enteral feeding was administered.

Clinical assessment

Patients underwent clinical assessment before and 3 months after GP. Clinical outcomes were analysed with the ^{13}C GEBT for GE analysis and with 24-hour pH monitoring for GER analysis. Additionally, parents and children without NI over 12 years of age filled out a reflux-specific questionnaire for GER symptoms.

Gastric emptying test

GE was assessed with the ^{13}C GEBT. For this ^{13}C GEBT, the stable isotope ^{13}C labeled Na-octanoate is added to a solid or liquid test meal. This test has proven to be a reliable, safe and non-invasive diagnostic method for GE in children. In contrast to 99mTc-Technetium scintigraphy, the former gold standard for GE, it offers normal values for children of all ages, both genders and liquid and solid intake. Additionally, ^{13}C GEBT does not involve radiation and is therefore suitable for large pediatric study populations.¹³ The intra-individual variability of the ^{13}C GEBT has been studied in multiple studies. Hauser *et al.* found a coefficient of intrasubject variation of 12.5, which was comparable to the results of other

studies. This variability is comparable with or even better than the variation reported by other techniques for GE measurement.¹⁴

Subjects fasted for at least 6 hours before the study. In children >4 years of age, a solid ¹³C-GEBT was performed with a 375-g pancake containing 45mg of ¹³C labeled Na-octanoate (a stable isotope). For younger children or children who were unable to eat the pancake within 15 minutes, 100mg of ¹³C labeled Na-octanoate was added to a liquid formula (infant formula, full cream milk or chocolate milk). Breath samples were obtained in duplicate at 15-minute intervals during the course of 4 hours (for the liquid test, breath samples were obtained at 5-minute intervals during the first 30 minutes). The ratio between ¹²CO₂ and ¹³CO₂ content in breath samples was analysed with an isotope ratio mass spectrometer.

With this ¹³C-GEBT, three parameters were calculated. Gastric half-emptying time (GE-T_{1/2}) was defined as the time when the first half of the ¹³C-labeled substrate had been metabolized, that is, when the cumulative excretion of ¹³C in the breath was half the ingested amount. GE percentiles (P) were calculated according to the reference values obtained by M. van den Driessche *et al.*¹⁵ GE percentiles higher than 95 were considered delayed. The GE coefficient (GEC) reflects a global index for GE, influenced by both the rate of appearance and disappearance of ¹³C in breath.

24-hour pH-monitoring

After 72-hour cessation of antireflux medication, ambulatory 24-hour pH-monitoring was thoracic X-ray performed. A single-use multichannel intraluminal impedance pH-catheter (Unisensor AG, Attikon, Switzerland) was calibrated in two different pH solutions and positioned transnasally into the distal esophagus with the probe located proximal to the lower esophageal sphincter. Correct catheter position was confirmed by For a 24-hour period, acidity values were recorded in an ambulatory recorder. In a symptom diary, mealtimes, symptoms, body position (supine and upright) and other relevant events (e.g. correction of the catheter position) were documented. Automated analysis was performed with software designed for pH impedance analysis (Medical Measurement Systems). Pathological esophageal acid exposure was defined as total acid exposure time $\geq 6\%$, $\geq 9\%$ in upright, and $\geq 3\%$ in the supine body position.¹⁶

Statistical analysis

Continuous variables were expressed as mean \pm standard deviations (SD) for symmetric variables or as median with interquartile ranges (IQR) for skewed variables. Pre- and postoperative results were compared using the McNemar's test for binary outcomes and the paired T-test for continuous outcomes. Associations between categorical data were

investigated with the Chi-Squared test or, in case of small-expected numbers, with the Fisher's exact test. Correlations of continuous data were investigated with the Pearson's correlation coefficient. Missing values were imputed using multiple imputation with 20 imputations. Descriptive statistics are reported for the original data; examination and testing of relations between variables was performed on the multiply imputed data.

Gastrostomy failure was defined as feeding intolerance or leakage at the gastrostomy site. Feeding intolerance was determined with the questionnaire that was filled out by parents scoring the vomiting symptoms of their child on a frequency scale (0–7 days a week) and a severity scale (0–7; **Table 1**). Patients with at least daily and moderately severe vomiting or at least weakly and severe vomiting (Grade 2 or 3) were considered feeding intolerant. Leakage at the gastrostomy site was determined by the indication for (re)admission or gastrojejunostomy placement. To identify parameters predictive of gastrostomy failure, logistic regression analysis was performed. Potential risk factors were: age, neurologic impairment, preoperative GE, acid exposure time and symptomatic GER.

To identify parameters predictive of postoperative GE, multiple linear regression analysis was performed. Variables included in the analysis were: age, NI, preoperative GE, acid exposure time and symptomatic GER. Statistical significance was defined by *p*-values of less than 0.05. All analyses were performed using SPSS 22.0 statistical package (IBM, USA).

Table 1. Scoring system that combines severity and frequency of symptoms of feeding intolerance.

	Severe	Moderate	Mild	Absent
Daily	Grade 3	Grade 2	Grade 1	Grade 0
Weekly	Grade 2	Grade 1	Grade 1	Grade 0
Monthly	Grade 1	Grade 1	Grade 1	Grade 0
Infrequent	Grade 1	Grade 1	Grade 1	Grade 0

RESULTS

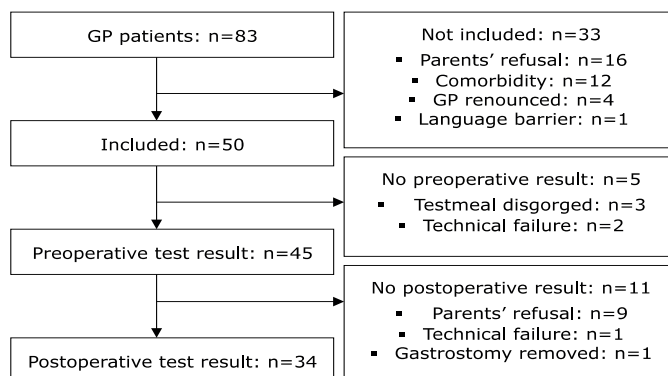
A total of 50 patients were included with a median age of 3.4 years (1.4 – 5.6). Indication for gastrostomy was insufficient oral caloric intake in 47 patients. The remaining 3 patients received a gastrostomy for administering laxatives in chronic obstipation. The main underlying pathologies were neurological disorder (68%) and cystic fibrosis (8%). Patient characteristics are described in **Table 2**.

Table 2. Patient characteristics

Demographics	
Total number of patients	50
	n (%)
Male gender	29 (58%)
	Median (IQR)
Age at time of operation (years)	3.4 (1.4– 5.6)
Follow-up time (months)	4.6 (3.7 – 5.6)
Main underlying disorder	n (%)
Neurologic impairment	34 (68%)
Cystic fibrosis	4 (8%)
Chronic obstipation	3 (6%)
Failure to thrive with unknown diagnosis	3 (6%)
Congenital cardiac disease	2 (4%)
Metabolic disorder	2 (4%)
Pulmonary disease	1 (2%)
Short bowel syndrome	1 (2%)

Legend: N: number; IQR: interquartile range.

Preoperative ^{13}C GEBT was performed successfully in 45 patients. In 34 of these patients ^{13}C GEBT was also completed successfully after operation (**Figure 1**). In nine patients, ^{13}C GEBT could not be repeated due to parents' refusal. These parents considered the postoperative test as too much of a burden. In one patient, the gastrostomy was removed two months after gastrostomy at the request of parents because of repetitive leakage at the gastrostomy site. One postoperative test could not be completed due to technical failure. Liquid ^{13}C GEBT was performed in 40 (89%) of the preoperative tests and in 32 (94%) of the postoperative tests; the remaining tests were performed with solid intake.

**Figure 1. Overview of patient inclusion.**

Legend: Technical failure: low CO₂ in air tubes. GP: gastrostomy placement; N: number

24-hour pH monitoring was performed in all patients before operation and repeated after gastrostomy in 28 patients (56%). All parents filled out the reflux-specific questionnaires.

Symptoms

Almost all patients (49/50) still received gastrostomy feeding at 3 months follow-up. The majority of patients (73%) were able to receive enteral feeding in boluses; the remaining 27% were dependent on continuous drip-feeding (either solely overnight or 24h per day). Seventy percent of patients with gastrostomy feeding received additional oral feeding; the other 30% of patients was entirely dependent on feeding through the gastrostomy tube. Gastrostomy failure, caused by leakage (n=6) and/or feeding intolerance (n=8), occurred in 10 patients (20%) after GP.

Gastroesophageal reflux

After GP, the acid exposure time remained similar (preoperative 6.1% (2.7 – 16.0) and postoperative 6.1% (2.8 – 12.1); $p=0.866$; $n=28$). Four patients (14%) developed pathological GER after GP, whereas pathological GER disappeared in the same number of patients. GER symptoms were present in a comparable number of patients before (44%) and after GP (39%) (McNemar $p=0.73$).

Gastric emptying

After gastrostomy, GE rate significantly decreased compared to preoperative GE rate: the GE percentile and the GE-T½ both significantly increased ($p<0.001$ and $p=0.03$, respectively) and the GEC decreased significantly ($p<0.001$)(**Table 3A**).

Table 3A. Gastric emptying before and after GP (n=50)

	Before GP	After GP	<i>p</i> -value ¹
GE percentile (SD)	57 (± 36.6)	79 (± 30.7)	<0.001
GEC (SD)	3.8 (± 0.90)	3.5 (± 0.86)	<0.001
GE-T½ (minutes; IQR)	45 (24 – 70)	71 (39 – 94)	0.03

Legend: 1. Paired T-test.

GE: gastric emptying; GEC: gastric evaluation coefficient; GE-T½: gastric half-emptying time; IQR: interquartile range; SD: standard deviation

In 26 patients (76.5%), GE was normal before operation. After gastrostomy, 50% of these 26 patients developed DGE (McNemar $p=0.01$; **Figure 2**). Before gastrostomy, DGE ($P>95$) was present in 8 patients. After operation, this number increased to 19 patients (56%; McNemar $p=0.01$).

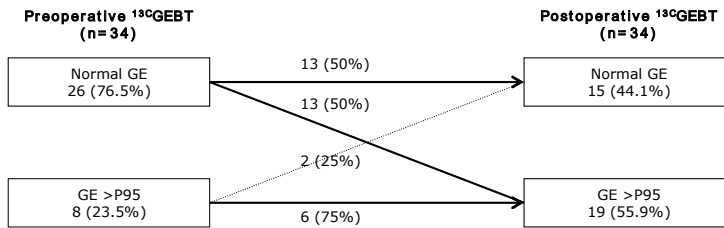


Figure 2. Gastric emptying before and after GP (n=34)

Legend: GE: gastric emptying; GP: gastrostomy placement; ¹³C GEBT: ¹³C-octanoic acid gastric emptying breath test; P: percentile

After dividing the patients into two subgroups: patients with NI and neurologically normal (NN) patients, subanalysis showed that NI patients had a higher GE percentile before operation (P62 (\pm 36.5) vs P57 (\pm 36.6)) (**Table 3B**). The GE percentile in NI patients significantly increased to P84 (\pm 27.9) after operation ($p < 0.001$), a similar increase compared to the NN patients.

Table 3B. Subanalysis of NI patients (n=34)

	Before GP	After GP	<i>p</i> -value ¹
GE percentile (SD)	62 (\pm 36.5)	84 (\pm 27.9)	0.004
GEC (SD)	3.9 (\pm 0.95)	3.5 (\pm 0.69)	0.004
GE-T _{1/2} (minutes; IQR)	44 (27 – 64)	66 (49 – 93)	0.03

Legend: 1. Paired *T*-test. GE: gastric emptying; SD: standard deviation; GEC: gastric evaluation coefficient; GE-T_{1/2}: gastric half-emptying time; IQR: interquartile range

Sequelae of DGE

A ¹³C GEBT was completed in 4 out of 6 patients with leakage after gastrostomy, all showing DGE (100%; Fisher's exact $p = 0.11$). In patients with feeding intolerance, postoperative ¹³C GEBT showed DGE in 6 out of 8 patients (75%; Fisher's exact $p = 0.25$).

A positive correlation was found between GE-T_{1/2} and esophageal acid exposure time, both before ($r = 0.28$; $p < 0.001$) and after GP ($r = 0.46$; $p < 0.001$) ($n = 28$). Increased acid exposure time after GP was correlated with increased GE-T_{1/2} ($r = 0.375$; $p < 0.001$). No significant correlation was found between postoperative GE-T_{1/2} and GER symptoms ($r = 0.016$; $p = 0.624$).

Risk factors

In univariable analysis of failure after GP, none of the characteristics examined were statistically significant predictors (**Table 4**).

Table 4. Predictors of gastrostomy failure – univariable analysis (n=50)

Predictors (preoperative)	p-value	Predictive value (odds)	95% CI
Age (years)	0.11	0.84	0.67 - 1.05
Acid exposure time (% / 24h)	0.17	0.93	0.85 - 1.03
Neurologic impairment (yes/no)	0.18	0.44	0.11 - 1.54
GE (percentile)	0.27	0.99	0.97 - 1.01
Symptomatic GER (GSQ)	0.50	1.01	0.98 - 1.04

Legend: GE: gastric emptying; CI: confidence interval; GER: gastroesophageal reflux; GSQ: gastroesophageal reflux symptom questionnaire

In multivariable analysis of postoperative GE, only the preoperative GE was a positive predictor (B=0.3; 0.04–0.6). Age and NI were not predictive of postoperative GE (Table 5).

Table 5. Predictors of postoperative GE percentile – multivariable analysis (n=50)

Predictors	p-value	Predictive value (B)	95% CI
Preoperative GE (percentile)	0.03	+0.3	+0.04 - +0.6
Neurologic impairment (yes/no)	0.32	+9.8	-9.5 - +29.2
Age (years)	0.71	+0.5	-2.0 - +3.0

Legend: GE: gastric emptying; CI: confidence interval

DISCUSSION

In this prospective pediatric study, we found that gastrostomy placement causes a significant decrease in GE rate. Fifty percent of patients with a normal preoperative GE develop DGE after GP.

This is the first prospective study on GE before and after GP involving pediatric patients. Only one previous study was published on this subject.¹¹ This was a retrospective study including 26 NI children undergoing laparoscopic GP. In contrast to our study, authors reported no significant changes in GE after operation. This might be due to the shorter follow-up time in that study of 6-13 days after surgery.

In adults, two studies have been performed on GE after GP, showing no significant changes. The first study reported a non-significant delay in GE-T½ in 11 patients.⁹ The second study found that GE was unaffected after GP.¹⁰ GE testing in this study was, however, conducted with the paracetamol absorption test, i.e. plasma concentrations of

paracetamol at 45 minutes after drug administration. This diagnostic technique still needs further standardization before it can reliably be used for research purposes.¹⁷

Furthermore, results of adult studies cannot be translated to the pediatric population, mainly because indications for GP differ. In the adult population, gastrostomy placements are primarily performed in patients with head and neck malignancies, whereas in the pediatric population, patients often suffer from profound neurological impairment.¹⁸ Generalized gastrointestinal dysmotility is frequently encountered in these patients^{19,20} and GI motility changes after GP may consequently differ. Well-designed studies confined to the pediatric population are therefore necessary.

The cause for the delay in GE is not evident. A previous study reported that myoelectrical activity, relevant to gastric motor function, was unaffected after GP.¹⁰ Slow fundic contractions are believed to transfer gastric contents from the fundus to the antrum for trituration and subsequent GE. These contractions might be affected by gastrostomy placement in the gastric body.²¹ To clarify the cause for delay in GE, motility tests such as three-dimensional ultrasonography or dynamic contrast-enhanced magnetic resonance imaging of the stomach may be useful.

The effect of a GP on GER has been a matter of profound debate. A systematic review showed that evidence has been inconsistent and of insufficient methodological quality.²² In our study, the total acid exposure time did not change significantly, supporting previous findings that GER generally does not worsen after GP.^{3,22,23}

DGE is associated with GER, based on the positive correlation between GE-T_{1/2} and acid exposure time, both before and after gastrostomy. This is in line with previous studies reporting on this pathophysiologic relationship.^{24,25} Furthermore, we found that changes in acid exposure time after GP were correlated to changes in GE. Thus, development or worsening of GER after GP, which was frequently reported by other studies^{26,27}, seems to be influenced by a delay in GE.²⁸ Other factors may also play a role in the pathogenesis of GER after gastrostomy, e.g. changes in lower esophageal sphincter pressure²⁹ or the presence of esophageal hiatus hernia.¹⁰

Postoperative DGE may stimulate problems such as leakage and intolerance of feeding. No previous studies have reported on this causality. According to our findings, most patients with complications of leakage and feeding intolerance were found to have postoperative DGE. Analysis in larger study populations is required to provide more certainty on the causality between DGE and gastrostomy failure.

Children undergo GP for a wide variety of indications. The majority of children in our cohort suffered from NI (68%). It is well known that these children often suffer from generalized gastrointestinal dysmotility.^{19,20} This may have resulted in slower GE in NI children compared to NN children in our cohort. For this reason we performed a subanalysis of NI children alone. It indeed showed a higher GE percentile before operation. However, after operation the delay in GE was similar (both NI and NN made an increase of 22 percentile-points).

Unfortunately, we were unable to identify preoperative predictors of gastrostomy failure. The number of patients with gastrostomy failure (n=12) was too low to perform multivariable analysis. The occurrence of gastrostomy failure might be multifactorial or dependent on factors not included in our univariable analysis.

To our knowledge, no previous study has identified predictors of gastrostomy failure in children. However, two studies attempted to identify predictors of all minor gastrostomy-related complications (including e.g. hypergranulation and stomal infection). The first study identified no significant predictors.⁶ The other reported a higher frequency of complications in patients with cardiac malformations (n=17).⁵ Future research dedicated to this subject may provide us with more insight into risk factors for complications after GP.

A limitation of this study was that 11 postoperative ¹³C GEBTs were missing. In order to maintain adequate statistical power, we performed multiple imputation analysis on ¹³C GEBT results. Analysis of the imputed data yielded results similar to those of the original data. This suggests a random missing of the postoperative ¹³C GEBT, therefore making a bias on the effect sizes less probable.

In conclusion, this is the first study that demonstrates a delay in GE after a GP in children. Patients with a normal preoperative GE have a 50% chance of developing DGE after GP. DGE after GP is associated with GER and is found in most patients with postoperative leakage and feeding intolerance. Although gastrostomy failure could not be predicted with preoperative data, the negative effect of GP on GE and its possible consequences should be taken into account when this operation is considered in pediatric patients.

REFERENCES

1. Sullivan PB, Juszczak E, Bachlet AM, et al. Gastrostomy tube feeding in children with cerebral palsy: a prospective, longitudinal study. *Dev Med Child Neurol* 2005; 47(2):77-85.
2. Mahant S, Friedman JN, Connolly B, et al. Tube feeding and quality of life in children with severe neurological impairment. *Arch Dis Child* 94(9):668-673.
3. Franken J, Mauritz FA, Suksamanapun N, et al. Efficacy and adverse events of laparoscopic gastrostomy placement in children: results of a large cohort study. *Surg Endosc* 2015; 29(6):1545-52.
4. Friedman JN, Ahmed S, Connolly B, et al. Complications associated with image-guided gastrostomy and gastrojejunostomy tubes in children. *Pediatrics* 2004; 114(2):458-461.
5. Arnbjornsson E, Larsson LT, Lindhagen T. Complications of laparoscopy-aided gastrostomies in pediatric practice. *J Pediatr Surg* 1999; 12-34(12):1843-1846.
6. Naiditch JA, Lautz T, Barsness KA. Postoperative complications in children undergoing gastrostomy tube placement. *J Laparoendosc Adv Surg Tech* 2010; 20(9):781-785.
7. Maddern GJ, Chatterton BE, Collins PJ, et al. Solid and liquid gastric emptying in patients with gastro-oesophageal reflux. *Br J Surg* 1985; 72(5):344-347.
8. Collins BJ, McFarland RJ, O'Hare MM, et al. Gastric emptying of a solid-liquid meal and gastrointestinal hormone responses in patients with erosive oesophagitis. *Digestion* 1986; 33(2):61-68.
9. Wakamatsu H, Nagamachi S, Nishii R, et al. Effect of percutaneous endoscopic gastrostomy on gastrointestinal motility: evaluation by gastric-emptying scintigraphy. *Nucl Med Commun* 2008; 29(6):562-567.
10. Ono H, Azuma T, Miyaji H, et al. Effects of percutaneous endoscopic gastrostomy tube placement on gastric antral motility and gastric emptying. *J Gastroenterol* 2003; 38(10):930-936.
11. Kawahara H, Tazuke Y, Soh H, et al. Does laparoscopy-aided gastrostomy placement improve or worsen gastroesophageal reflux in patients with neurological impairment? *J Pediatr Surg* 2014; 49(12):1742-1745.
12. Haans JJ, Masclee AA. Review article: The diagnosis and management of gastroparesis. *Aliment Pharmacol Ther* 2007; 26 Suppl 2:37-46.
13. Eradi B, Wright J, Gibbons NJ, et al. Validity of ¹³C octanoic acid breath test for measurement of solid meal gastric emptying time in children. *J Pediatr Surg* 2006; 41(12):2062-2065.
14. Hauser B, De Schepper J, Caveliers V, et al. Variability of the ¹³C-octanoic acid breath test for gastric emptying of solids in healthy children. *Aliment Pharmacol Ther* 2006; 23(9): 1315-1319.
15. Van den Driessche ML, Veereman-Wauters GA, Ghooys Y. Development of gastric emptying in healthy infants and children and reference values for the ¹³C octanoic acid breath test. *Gastroenterology* 2000; 118(4):A392.
16. Richter JE, Bradley LA, DeMeester TR, et al. Normal 24-hr ambulatory esophageal pH values. Influence of study center, pH electrode, age, and gender. *Dig Dis Sci* 1992; 37(6):849-856.
17. Willems M, Quartero AO, Numans ME. How useful is paracetamol absorption as a marker of gastric emptying? A systematic literature study. *Dig Dis Sci* 2001; 46(10):2256-2262.
18. Srinivasan R, Irvine T, Dalzell M. Indications for percutaneous endoscopic gastrostomy and procedure-related outcome. *J Pediatr Gastroenterol Nutr* 2009; 49(5):584-588.

19. Del Giudice E, Staiano A, Capano G, et al. Gastrointestinal manifestations in children with cerebral palsy. *Brain Dev* 1999; 21(5):307-311.
20. Sullivan PB. Gastrointestinal disorders in children with neurodevelopmental disabilities. *Dev Disabil Res Rev* 2008;14(2):128-136.
21. Nguyen NQ, Fraser RJ, Bryant LK, et al. Functional association between proximal and distal gastric motility during fasting and duodenal nutrient stimulation in humans. *Neurogastroenterol Motil* 2007; 19(8):638-645.
22. Noble LJ, Dalzell AM, El-Matary W. The relationship between percutaneous endoscopic gastrostomy and gastro-oesophageal reflux disease in children: a systematic review. *Surg Endosc* 2012; 26(9):2504-2512.
23. Launay V, Gottrand F, Turck D, et al. Percutaneous endoscopic gastrostomy in children: influence on gastroesophageal reflux. *Pediatrics* 1996; 97(5):726-728.
24. Sager S, Halac M, Selcuk N, et al. Temporal relationship between gastroesophageal reflux and rate of gastric emptying in children. *Nucl Med Commun* 2010; 31(12):1059-1062.
25. Estevao-Costa J, Campos M, Dias JA, et al. Delayed gastric emptying and gastroesophageal reflux: a pathophysiologic relationship. *J Pediatr Gastroenterol Nutr* 2001; 32(4):471-474.
26. Khattak IU, Kimber C, Kiely EM, et al. Percutaneous endoscopic gastrostomy in paediatric practice: complications and outcome. *J Pediatr Surg* 1998; 33(1):67-72.
27. Heine RG, Reddihough DS, Catto-Smith AG. Gastro-oesophageal reflux and feeding problems after gastrostomy in children with severe neurological impairment. *Dev Med Child Neurol* 1995; 37(4):320-329.
28. Razeghi S, Lang T, Behrens R. Influence of percutaneous endoscopic gastrostomy on gastroesophageal reflux: a prospective study in 68 children. *J Pediatr Gastroenterol Nutr* 2002; 35(1):27-30.
29. Jolley SG, Tunell WP, Hoelzer DJ, et al. Lower esophageal pressure changes with tube gastrostomy: a causative factor of gastroesophageal reflux in children? *J Pediatr Surg* 1986; 21(7):624-627.

Chapter 5

Gastrostomy placement in children does not increase gastroesophageal reflux.

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ABSTRACT

Introduction: A gastrostomy placement (GP) is frequently performed in pediatric patients who require long-term enteral tube feeding. Current evidence on the relation between GP and the development of postoperative gastroesophageal reflux has been inconsistent. The aim of this study is to investigate the influence of GP on GER with 24-hour multichannel intraluminal impedance pH monitoring (MII-pH monitoring).

Methods: A prospective, longitudinal cohort study was performed including 50 patients who underwent laparoscopic GP between May 2012 and April 2014. Caregivers filled out GER symptom questionnaires and 24-hour MII-pH monitoring was performed before and 3 months after surgery.

Results: Twenty-five out of 50 included patients (50%) underwent both the preoperative and postoperative tests and were included in MII-pH analysis. Total acid exposure (percentage of time with pH below 4) did not change significantly after GP: from 6.2% (3.0 – 18.1) to 6.1% (2.6 – 14.9). The number of reflux episodes did not significantly change, for either liquid (mean difference 4.3 (-4.5 – 13.2)) or mixed liquid-gas reflux (mean difference 2.0 (-9.3 – 13.3)). Before GP, 18 out of 25 patients had pathological GER (72%). This percentage of patients did not change after GP (72%): In four patients pathological GER dissolved, whereas four patients newly developed pathological GER. A low preoperative weight-for-height percentile was associated with increased acid exposure after GP.

Conclusion: Overall, GP did not induce GER in children.

INTRODUCTION

A gastrostomy placement (GP) is an effective procedure that provides long-term enteral tube feeding in children with feeding difficulties.^{1,2} The main underlying diseases that require GP are neurological impairment (NI), cystic fibrosis and congenital cardiac disease.^{3,4} GP enables successful feeding in 96% of patients,⁴ however, it is not without complications. Complications such as leakage and gastrostomy site infection are commonly seen and described.⁵

The development or deterioration of gastroesophageal reflux (GER) after GP is a widely discussed adverse event of GP.⁶ It is important to consider the effect of GP on GER since a high proportion of patients who receive GP have impaired neurodevelopment^{3,5} and are therefore already at risk of GER.⁷ Possible consequences of GER in pediatric patients include esophagitis and aspiration with or without pneumonia.⁸ Furthermore, chronic GER is a risk factor for the development of Barrett esophagus and adenocarcinoma of the esophagus.⁹ Due to its widespread consequences, it is important to evaluate if GP increases GER in children. Although in most cases children have few alternatives for GP, patients, caregivers and pediatric surgeons need to know the consequences of this operation.

Few prospective studies have used 24-hour pH metry to compare pre- and postoperative GER after GP.⁶ While some studies suggest a worsening or development of esophageal acid exposure after operation^{7,10} others show no change or even decrease in GER.^{11,12} The majority of evidence has been of low quality, as described in detail by a systematic review of Noble *et al.*⁶ Consequently, no consensus currently exists on the topic of GER and GP.

Until recently, pH monitoring was considered the gold standard for GER measurement. However, the development of multichannel intraluminal impedance (MII) combined with pH monitoring has greatly improved diagnostic possibilities of GER in both children and adults.¹³⁻¹⁵ This technique detects changes in electrical impedance between two electrodes during the passage of a bolus. The main advantage of MII-pH over traditional pH monitoring is the ability to detect acid, weakly acidic and non-acid reflux episodes and to differentiate between liquid and gas movements within the esophageal lumen.^{15,16} It has been demonstrated that most reflux episodes occurring in children are undetectable by standard pH-only monitoring. Combining pH monitoring with MII is therefore valuable and possibly superior to pH-only measurements especially when diagnosing GER in children.¹⁷

The aim of this study is to evaluate the effect of GP on GER in children with the 24-hour MII-pH monitoring.

METHODS

Study design

A prospective, longitudinal cohort study was performed including pediatric patients who underwent GP in the Wilhelmina Children's Hospital between May 2012 and April 2014. Exclusion criteria were refusal or inability of patients or caregivers to undergo the clinical tests, technical failure of 24-hour MII-pH metry and/or removal of the gastrostomy. Patient characteristics of non-responders were also recorded for adequate comparison of both patient groups. Patients underwent clinical assessment for GER before and 3 months after surgery.

Ethical approval and trial registration

This study was part of a larger trial on GP in children, registered under the name of 'The effect of laparoscopic gastrostomy on gastric emptying: A prospective observational study in children.' at the Netherlands Trial Registry (NTR3314, 29-02-2012). Ethical approval was obtained from the University Medical Centre Utrecht Ethics Committee. Prior to initiating any study procedure, informed consent was obtained from the patients' caregivers and the patients themselves, when 12 years or older and without NI.

Surgical procedure

Laparoscopic GP was performed under general anaesthesia in all children. All procedures were performed or supervised by an experienced pediatric surgeon. An infra-umbilical 6 mm trocar was introduced for the camera. The position of the gastrostomy was determined between the umbilicus and the costal margin. A small incision was made introducing a Babcock clamp to grasp the ventral wall of the gastric corpus under direct laparoscopic view. After pulling up the corpus, the gastric wall was sutured to the fascia of the abdominal wall with four interrupted Vicryl 4-0 sutures. After insufflation of the stomach, a needle was inserted through the stomach wall. Using the Seldinger technique, a peel-away dilator was placed followed by insertion of a gastrostomy tube. The gastrostomy balloon was inflated with sterile water.

Clinical assessment

Patients underwent clinical assessment before and 3 months after surgery. GER analysis was performed with a reflux-specific symptom questionnaire and 24-hour MII-pH monitoring. Additionally, gastric emptying tests were performed with the ¹³C-octanoic acid breath test.¹⁸ Data regarding feeding regimen, alternative feeding tube, weight and height, complications and reinterventions were collected with a gastrostomy-specific questionnaire.

GER symptom questionnaires

For symptom evaluation of GER in children, an age-specific reflux questionnaire was used: the GER Symptom Questionnaire (GSQ).¹⁹ In infants, symptoms assessed were back arching, choking or gagging, hiccups, irritability, refusal to feed and vomiting or regurgitation. In young children, symptoms assessed were abdominal pain, burping or belching, choking when eating, difficulty swallowing, refusal to eat, vomiting and regurgitation. In this questionnaire parents scored the symptoms of their child on a frequency scale (0–7 days a week) and a severity scale (0–7). Patients with at least daily and moderately severe symptoms, or at least weakly and severe symptoms were considered positive for GER symptoms.

24-hour MII-pH monitoring

Ambulatory 24-hour MII-pH monitoring was performed after 72-hour cessation of acid-suppressing medication or prokinetic medication. A single-use multichannel intraluminal impedance pH-catheter (Unisensor AG, Attikon, Switzerland) was calibrated using pH 4.0 and pH 7.0 buffer solutions and positioned transnasally into the distal esophagus with the probe located proximal to the lower esophageal sphincter (LES). Correct catheter position was confirmed with thoracic X-ray. This catheter has a single antimony pH electrode and six ring electrodes for recording of impedance signals, located at 3, 5, 7, 9, 11 and 13 cm from the distal tip of the probe for children below the age of 8 and at 3, 5, 7, 9, 15 and 17 cm for children above the age of 8. For a 24-hour period, acidity and impedance signals were recorded in a digital ambulatory recorder, using a sampling frequency of 50 Hz. Mealtimes, symptoms, body position (supine and upright) and other relevant events (e.g. correction of the catheter position) were documented in a symptom diary.

24-hour MII-pH monitoring: data analysis

Analysis was performed with software designed for MII-pH impedance analysis (Medical Measurements Systems, Enschede, the Netherlands). Meals were excluded from the analysis.

Automated analysis of pH tracings resulted in the following values, all representing traditional reflux measurements: total 24-hour esophageal acid exposure time (defined as the total time with pH below 4 divided by the time of monitoring), number of reflux episodes with pH below 4, number of reflux episodes lasting longer than 5 minutes, longest reflux episode and lowest pH value.

Pathological esophageal acid exposure was defined as total acid exposure time $\geq 6\%$, $\geq 9\%$ in upright, and $\geq 3\%$ in supine body position. These values are used by most centers and based on a large study by Richter *et al.*²⁰

MII tracings detect refluxes of boluses (either liquid or mixed liquid-gas) in the most distal channels irrespective of pH changes. The data was analyzed according to previously described definitions.^{21,22} All MII measurements were manually analyzed by one single observer (JF). In case of uncertainty, another expert observer was consulted (FAM and/or MH).

Liquid reflux was defined as a fall in impedance of more than 50% of baseline impedance that moved in the retrograde direction over the two distal impedance sites. Mixed liquid-gas reflux was defined as gas reflux occurring during or immediately preceding liquid reflux. For adequate comparison, the number of reflux episodes was normalized to a 24-hour period.

Reflux episodes were classified as acid when the pH dropped below 4; reflux episodes were classified as weakly acidic when the lowest pH was between 4 and 7; and as non-acid when pH remained above 7.

Reflux episodes were also classified based on the most proximal impedance channel demonstrating an impedance drop of more than 50% from baseline: as proximal (reaching Z1), mid-esophageal (reaching Z3) or distal (reaching Z5).

The bolus clearance time was defined as the elapsed time from onset to recovery of the impedance signal recorded on the most distal impedance channel (Z6).²³

If symptoms were recorded, the symptom index (SI) and symptom association probability index (SAP) were calculated for all reflux episodes, with an SI of more than 50% and an SAP of more than 95% regarded as being positive.

Nutritional status

Weight and height measurements were converted to weight-for-height and height-for-age percentiles based on the Netherlands Organization for Applied Scientific Research (TNO) growth standards.²⁴ These percentiles allow comparison of an individual's weight or height, adjusting for age and sex relative to a reference population.

Statistical analysis

Variables were not normally distributed and therefore expressed as median with interquartile ranges (IQR 25-75th). To test differences between participants and non-participants in the MII-pH study, independent-samples t-tests were used for continuous variables and Fisher's exact tests for dichotomous variables. To express the effect of surgery the paired t-test was used for paired, continuous data where differences were normally distributed. The

McNemar test was used for paired categorical data. Correlations of continuous data were investigated with the Spearman's correlation coefficient.

Multiple linear regression analysis was performed to identify parameters predictive of change in acid exposure after operation. Variables included in the analysis were based on univariable analysis and included: age, neurologic impairment and weight-for-height percentile.

Statistical significance was, when possible, expressed by 95% confidence intervals. Where p -values were used, statistical significance was defined by p -values of less than 0.05. All analyses were performed using SPSS 24.0 statistical package (IBM, USA).

RESULTS

In total 50 patients were included and successfully underwent preoperative 24-hour MII-pH metry. Caregivers of all patients filled out the reflux questionnaires. Out of these 50 patients, postoperative 24-hour MII-pH monitoring was successfully performed in 25 patients (50%). In 20 out of the 25 patients without a postoperative test the reason was refusal by the caregivers or inability of the children to undergo the postoperative tests. A total of 25 patients were included in the analysis of MII-pH test results. The flowchart of patient inclusion is depicted in **Figure 1**.

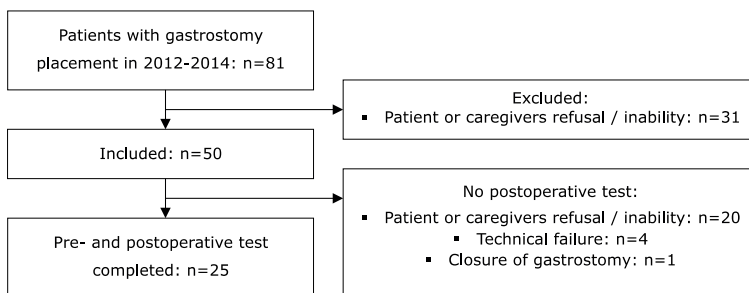


Figure 1. Flowchart of patient inclusion.

Patient characteristics of both participants and non-participants in the MII-pH study are described in **Table 1**. Median follow-up time after GP was 3.9 months (IQR 3.6 – 4.9). Mortality rate during follow-up was 0%. In one out of 25 patients the gastrostomy was removed because of recurrent leakage at the gastrostomy site leading to persistent local infection.

To analyze differences between participants and non-participants in the MII-pH study, analysis of GER symptoms and nutritional status was performed for both patient groups, shown in **Appendix 1**.

Symptom analysis according to GSQ

GER symptoms, reported by the GSQ, were present in a comparable number of patients before GP (11 / 25 = 44%) and after GP (10 / 25 = 40%; McNemar $p = 0.73$).

Table 1. Patient characteristics.

	Responders in MII-pH analysis (n=25)	Non-responders (only symptom analysis; n=25)	Difference
	n (%) or median (IQR)	n (%) or median (IQR)	
Male gender	17 (68%)	12 (48%)	$p = 0.25$ ¹
Age in years at operation	3.2 (1.2 – 5.6)	4.7 (1.5 – 8.7)	$p = 0.10$ ²
Weight-for-height percentile	30 (1.0 – 85.0)	14 (0.6 – 84.0)	$p = 0.16$ ²
Height-for-age percentile	2 (0.6 – 16.0)	8.0 (0.6 – 30.0)	$p = 0.33$ ²
Main underlying pathology			
Neurologic impairment	20 (80%)	16 (64%)	$p = 0.35$
Cystic fibrosis	1 (4%)	3 (12%)	NA
Undiagnosed FTT	1 (4%)	1 (4%)	NA
Short bowel disease	1 (4%)	1 (4%)	NA
Pulmonary disease	1 (4%)	0	NA
Cardiac disease	0	1 (4%)	NA
Metabolic disorder	1 (4%)	0	NA

Legend: ¹ Fisher's exact test. ² Independent samples t-test

CF: Cystic fibrosis; FTT: failure to thrive; IQR: interquartile range; NA: not applicable

24-hour MII-pH monitoring

Results of the 25 patients with 24-hour MII-pH monitoring are summarized in **Table 2**. Analysis of the pH-metry data showed that none of the parameters significantly changed after GP. The median total acid exposure remained unchanged after operation: 6.2% (3.0 – 18.1) to 6.1% (2.6 – 14.9).

Almost all reflux parameters decreased, but this change was not statistically significant. Conversely, the parameters on impedance analysis all increased, although again none of the parameters changed significantly. There were no changes in liquid reflux and mixed liquid-gas reflux. Similarly, acid reflux and weakly acid reflux did not differ. Neither the proximal extend of the reflux boluses nor the bolus clearance time in the distal esophagus (Z6) changed after GP.

Table 2. Results of 24-hour MII-pH monitoring for all patients combined (n=25)

	Preoperative (median IQR)	Postoperative (median IQR)	Mean difference (95% CI) ^{1,2}
I. pH analysis			
Total acid exposure per 24 hour (%)	6.2 (3.0 – 18.1)	6.1 (2.6 – 14.9)	-0.3 (-5.4 – 4.8)
Supine position	4.8 (0.8 – 21.7)	5.4 (2.2 – 14.6)	-1.2 (-6.1 – 3.6)
Upright position	4.9 (0.6 – 14.0)	5.1 (1.6 – 14.4)	-0.4 (-4.3 – 3.5)
Number of reflux episodes	57.1 (20.9 – 67.9)	32.3 (18.2 – 58.5)	-13.6 (-37.6 – 10.4)
Number of episodes > 5 min.	2.3 (0.4 – 9.1)	2.2 (1.2 – 7.5)	-1.1 (-3.6 – 1.4)
Longest reflux episode (min.)	10.1 (4.8 – 39.2)	18.9 (8.1 – 29.0)	-3.5 (-18.6 – 11.6)
Lowest pH	0.7 (0.45 – 1.0)	0.9 (0.6 – 1.1)	+0.1 (-0.3 – 0.3)
II. Impedance analysis			
Total reflux episodes per 24 hour	55.8 (38.5 – 77.5)	61.1 (31.4 – 89.1)	+8.7 (-11.0 – 28.3)
Acid	44.0 (19.6 – 64.4)	33.9 (13.9 – 66.5)	+2.4 (-14.5 – 19.3)
Weakly acidic	13.7 (7.5 – 24.7)	18.3 (8.0 – 33.0)	+5.3 (-1.4 – 12.1)
Liquid reflux	28.6 (16.8 – 46.6)	35.9 (12.2 – 48.5)	+4.3 (-4.5 – 13.2)
Acid	18.3 (9.6 – 33.2)	17.0 (6.4 – 34.1)	+2.4 (-6.9 – 11.7)
Weakly acidic	7.8 (4.7 – 16.6)	8.7 (5.0 – 21.7)	+2.0 (-0.9 – 4.9)
Mixed reflux	24.9 (17.2 – 36.8)	23.2 (14.7 – 39.4)	+2.0 (-9.3 – 13.3)
Acid	18.1 (8.8 – 31.6)	18.5 (6.7 – 29.8)	+0.01 (-9.6 – 9.6)
Weakly acidic	6.0 (2.6 – 10.5)	8.0 (1.7 – 15.0)	+2.9 (-2.1 – 7.9)
Proximal extend (% of episodes)			
Z1 (proximal esophagus)	29.0 (12.5 – 35.0)	22.0 (15.5 – 37.3)	+1.6 (-7.0 – 10.1)
Z3 (mid esophagus)	68.0 (56.0 – 81.0)	74.5 (59.3 – 83.0)	+5.0 (-2.4 – 12.5)
Z5 (distal esophagus)	100 (100 – 100)	100 (100 – 100)	NA
BCT in Z6 (sec.)			
Upright	17.3 (13.9 – 20.1)	14.7 (11.8 – 17.7)	+0.7 (-4.5 – 5.8)
Supine	16.1 (14.1 – 18.7)	14.1 (11.5 – 19.0)	-0.5 (-5.4 – 4.4)
Supine	16.1 (12.0 – 22.5)	15.6 (9.8 – 23.4)	+0.9 (-5.1 – 7.0)
SI >50%	4 / 13 (30.8%)	5 / 17 (29.4%)	
SAP >95%	6 / 13 (46.2%)	6 / 17 (35.3%)	

Legend: ¹ Paired samples t-test. ² McNemar.

NA = not applicable; IQR = interquartile range; 95% CI = 95% confidence interval.

GER symptoms on MII-pH analysis

The SI and SAP were low in the majority of patients who completed the diary during MII-pH analysis. Pathological GER on MII-pH analysis was not associated with either preoperative ($p = 1.00$) or postoperative ($p = 0.66$) GER symptoms in the GSQ.

Pathological GER

The total number of patients with pathological GER did not change: 18 out of 25 patients before operation (72%) and 18 out of 25 patients after operation (72%; $p=1.00$). Four

patients without preoperative GER developed pathological GER after operation, and in four patients GER dissolved. No patients showed a deterioration of GER that required fundoplication during follow-up.

Subgroup analysis: patients with preoperative pathological GER versus no pathological GER

In 18 out of 25 patients pathological GER (72%) was found with MII-pH analysis. MII-pH analysis showed that all pH parameters in the 18 patients seemed to decrease and impedance parameters seemed to increase, although none of these changes were statistically significant (**Table 3A**). The complete table with all MII-pH parameters in these patients is depicted in **Appendix 2a**.

Table 3A. 24-hour MII-pH monitoring: patients with preoperative pathological reflux (n=18).

	Preoperative median (IQR)	Postoperative median (IQR)	Mean difference (95% CI) ¹
I. pH analysis			
Total acid exposure per 24 hour (%)	10.8 (5.7 – 23.1)	8.8 (3.5 – 21.7)	-1.1 (-8.3 – 6.1)
Number of reflux episodes (pH<4)	59.9 (49.8 – 78.3)	50.0 (31.5 – 72.7)	-16.1 (-49.8 – 17.6)
Number of episodes > 5 min.	5.4 (1.5 – 25.4)	4.1 (1.2 – 11.2)	-2.0 (-5.4 – 1.4)
II. Impedance analysis			
Total reflux episodes per 24 hour	73.1 (49.4 – 83.5)	75.5 (47.6 – 127.7)	14.8 (-14.1 – 43.7)
Acid	53.8 (43.3 – 70.2)	54.5 (30.6 – 74.1)	5.4 (-20.0 – 30.8)
Weakly acidic	18.1 (8.8 – 24.7)	25.1 (8.6 – 35.0)	8.0 (-1.5 – 17.6)

Legend: 1. Paired samples t-test. BCT = bolus clearance time; GER = gastroesophageal reflux; IQR = interquartile range; NA = not applicable; 95% CI = 95% confidence interval.

In 7 out of 25 patients MII-pH metry showed no pathological GER (38%). Four out of these 7 patients (57.1%) newly developed pathological GER after operation.

MI-pH analysis showed that, total acid exposure in these 7 patients increased slightly after operation with a mean difference of 1.9% (0.1 – 3.8; **Table 3B**). Similarly, the number of reflux episodes lasting longer than 5 minutes increased with a mean difference of 1.3 (0.2 – 2.4). The complete table with all MII-pH parameters in these patients is depicted in **Appendix 2b**.

Table 3B. 24-hour MII-pH monitoring: patients without preoperative pathological reflux (n=7).

	Preoperative median (IQR)	Postoperative median (IQR)	Mean difference (95% CI) ¹
I. pH analysis			
Total acid exposure per 24 hour (%)	1.3 (0.6 – 2.6)	2.5 (1.6 – 7.5)	1.9 (0.1 – 3.8)
Number of reflux episodes (pH<4)	11.6 (6.1 – 41.2)	17.0 (8.5 – 19.2)	-7.0 (-26.2 – 12.2)
Number of episodes > 5 min.	0.0 (0.0 – 1.2)	1.3 (1.1 – 2.2)	1.3 (0.2 – 2.4)
II. Impedance analysis			
Total reflux episodes per 24 hour	31.6 (23.6 – 38.8)	25.6 (17.9 – 38.2)	-4.3 (-21.0 – 12.3)
Acid	18.2 (4.1 – 25.0)	10.2 (8.1 – 21.5)	-3.8 (-14.1 – 6.4)
Weakly acidic	13.5 (6.2 – 27.5)	7.9 (5.7 – 17.1)	-0.3 (-8.8 – 8.2)

Legend: 1. Paired samples *t*-test was used when differences were normally distributed. BCT = bolus clearance time; GER = gastroesophageal reflux; IQR = interquartile range; NA = not applicable; CI = confidence interval.

Predictors of increased acid exposure after GP

In multivariable regression analysis of increased acid exposure after GP, preoperative weight-for-height percentile was a negative predictor, with a predictive value (B) of -0.5 (95% CI -0.28 – -0.1), indicating that low preoperative weight-for-height predicts an increase in acid exposure after GP. Not predictive of acid exposure were age (B -0.1 (-2.0 – 0.9)) and NI (B -0.3 (-19.7 – 1.5)).

Gastric emptying in correlation to GER

The preoperative gastric half-emptying time was correlated to both the preoperative total acid exposure ($r_s=0.43$; $p=0.04$) and the number of reflux episodes ($r_s=0.46$; $p=0.03$) (Table 4). After GP no correlation was found between postoperative gastric emptying and reflux parameters.

Table 4. Correlations between MII-pH monitoring and gastric emptying (n=25).

Correlations	Preoperative T _{1/2} ¹		Postoperative T _{1/2} ²		Increase in T _{1/2} ³	
	r_s	p -value	r_s	p -value	r_s	p -value
Total acid exposure per 24 hour (%)	0.43	0.04	0.10	0.65	0.49	0.03
Nr of reflux episodes	0.46	0.03	0.12	0.59	0.13	0.58
Nr of episodes > 5 minutes	0.27	0.27	0.35	0.11	0.47	0.03
Longest reflux episode	0.23	0.30	0.21	0.35	0.28	0.23

Legend: ¹. Calculated with preoperative reflux values. ². Calculated with postoperative reflux values. ³. Calculated with increase in reflux values.

T_{1/2} = gastric half-emptying time converted to percentiles. r_s = Spearman correlation coefficient.

Postoperative *increase* in gastric half-emptying time was correlated with both an increase in total acid exposure and an increase in number of reflux episodes lasting longer than 5 minutes ($p=0.03$ and $p=0.03$).

Nutritional status

Weight-for-height scores did not significantly change during the follow-up period of 3.9 months: from the 30.0th percentile (1.0 – 85.0) to the 55.0th percentile (25.0 – 82.0) with a mean difference of 5.2 (-8.3 – 18.8). Similarly, height-for-age scores did not significantly change: from the 2.0th percentile (0.6 – 16.0) before operation to the 8.0th percentile (0.4 – 25.0) after operation with a mean difference of 2.9 (-1.9 – 7.7)

There was no correlation between acid exposure time and either weight-for-height percentiles (r_s 0.18; $p=0.42$) or height-for-age percentiles (r_s 0.15; $p=0.48$).

DISCUSSION

This prospective, longitudinal cohort study demonstrated that laparoscopic GP does not cause an overall increase in GER on 24-hour MII-pH monitoring. The total number of patients with pathological GER remained similar after operation. Although all pH-metry reflux parameters decreased and all MII parameters increased, none of these changes were statistically significant. These results underline the hypothesis that GP is not associated with an increase in pathological GER.

Previous studies on this subject have been contradictory. While some studies suggest a worsening or development of esophageal acid exposure after operation^{7,10} other studies show no change or decreased GER.^{11,12} In line with our findings on pH-metry, Kawahara *et al.* found that that esophageal acid exposure increased in patients without pathological GER after GP on traditional 24-hour pH monitoring, but decreased in those with pathological GER.²⁵

Previous studies were performed using conventional 24-hour pH metry. In this current study we used 24-hour MII-pH metry, enabling us to detect passage of acid reflux, weakly acidic and non-acid reflux, as well as liquid refluxes and mixed liquid–gas refluxes. In children weakly and non-acidic reflux occur more frequently compared to the adult population²⁶ and these cannot be detected by conventional 24-pH metry. Analysis of MII tracings in our cohort did not identify a significant change in GER after GP in the cohort as a whole.

Consequently, after using the most accurate method for GER analysis, we can now more certainly say that GP in general is not associated with an increase in pathological GER.

Many children requiring GP have coexistent GER, especially those with NI.²⁷ This is also found in our study showing a high percentage of pathological GER before GP (72%). In earlier days it was suggested that in children with pathological GER before GP a concomitant fundoplication was needed, even though this operation is associated with possible additional adverse event.²⁸ In our current study none of the patients with postoperative pathological reflux required antireflux surgery during follow-up. Moreover, in 22% of patients with preoperative pathological GER, this pathological GER had disappeared after GP. This is in line with two other studies that showed that pathological GER dissolved in a significant number of patients after GP without concomitant fundoplication.^{12,29} These results justify that routine fundoplication in present day is no longer used as a standard procedure in children with pathological GER on preoperative measurements. As a result, routine preoperative workup for GP does not have to include assessment studies for GER.

In subgroup analysis of patients without preoperative GER, total acid exposure and the number of reflux episodes lasting longer than 5 minutes increased slightly. It is questionable whether these small differences of 1.9% (0.1 – 3.8) and 1.3 (0.2 – 2.4) are clinically relevant. However, it is noteworthy that GER seems to slightly increase in some patients without preoperative pathological GER.

We found that children with poor preoperative nutritional status were at greater risk of an increase in acid exposure after operation. Age and neurologic impairment were not predictive of increased acid exposure.

GER symptoms reported in the GSQ were not associated with pathological GER on MII-pH analysis. Similarly, symptom association in the MII-pH metry was low in the majority of patients. This is consistent with current knowledge: many of the reflux episodes detected with diagnostic tests go unnoticed clinically; conversely, not all symptoms are detected on diagnostic tests.³⁰ This underlines the importance of reliable diagnostic tests for GER.

We found that preoperative total acid exposure was correlated with preoperative gastric half-emptying time. Also, an increase in the one correlated with an increase in the other. These results suggest that delayed GE may influence the occurrence of GER after GP. However, postoperative values did not correlate. Delayed gastric emptying has been thought to accentuate postprandial reflux by increasing the volume of refluxate per episode of reflux (through an incompetent lower esophageal sphincter).³¹ Our results support the hypothesis that delayed GE is one of the pathogenic factors of GER in children.

In analysis of nutritional status, the increase in weight-for-height percentiles did not reach statistical significance. This may be caused by our follow-up time of 3 months, which may have been too short to demonstrate significant weight gain. A retrospective survey of 300 children undergoing GP in our institute with a follow-up time of 2.63 years demonstrated a significant increase in weight-for-height percentile ($p < 0.0005$).

Limitation of this study was that 50% of patients with initial preoperative evaluation of GER did not undergo the postoperative test and could not be included in our analysis of MII-pH results. Most of these missing patients were caused by refusal or inability of children or caregivers to participate in the postoperative tests, mainly because of the need for readmission to the hospital and anticipated burdening of the child. There were no differences between participants and non-participants with regard to main underlying pathology and preoperative weight-for-height values and height-for-age values. Furthermore, postoperative changes in GER symptoms and weight and height values were similar in the non-responders group.

In conclusion, GER is frequently encountered in children undergoing GP, especially in children with NI. The relationship between GP and the occurrence of GER is complex. In this study we presented results of a prospective evaluation of GER before and after GP with 24-hour MII-pH monitoring. GER was slightly aggravated in patients without preoperative pathological GER, while pathological GER disappeared in other patients after GP. In conclusion, overall, GP does not induce GER.

REFERENCES

1. Ferluga ED, Sathe NA, Krishnaswami S, et al. Surgical intervention for feeding and nutrition difficulties in cerebral palsy: A systematic review. *Developmental Medicine & Child Neurology*. 2014;56(1):31-43.
2. Craig GM, Carr LJ, Cass H, et al. Medical, surgical, and health outcomes of gastrostomy feeding. *Dev Med Child Neurol*. 2006;48(5):353-360.
3. Srinivasan R, Irvine T, Dalzell M. Indications for percutaneous endoscopic gastrostomy and procedure-related outcome. *J Pediatr Gastroenterol Nutr*. 2009;49(5):584-588.
4. Franken J, Mauritz FA, Stellato RK, Vet al. The effect of gastrostomy placement on gastric function in children: A prospective cohort study. *J Gastrointest Surg*. 2017 Jul;21(7):1105-1111.
5. Franken J, Mauritz FA, Suksamanapun N, Hulsker CC, et al. Efficacy and adverse events of laparoscopic gastrostomy placement in children: Results of a large cohort study. *Surg Endosc* 2015 Jun;29(6):1545-52
6. Noble LJ, Dalzell AM, El-Matary W. The relationship between percutaneous endoscopic gastrostomy and gastro-oesophageal reflux disease in children: A systematic review. *Surg Endosc*. 2012;26(9):2504-2512.
7. Heine RG, Reddihough DS, Catto-Smith AG. Gastro-oesophageal reflux and feeding problems after gastrostomy in children with severe neurological impairment. *Dev Med Child Neurol*. 1995;37(4):320-329.
8. Srivastava R, Downey EC, O’Gorman M, et al. Impact of fundoplication versus gastrojejunal feeding tubes on mortality and in preventing aspiration pneumonia in young children with neurologic impairment who have gastroesophageal reflux disease. *Pediatrics*. 2009;123(1):338-345.
9. Shaheen N, Ransohoff DF. Gastroesophageal reflux, barrett esophagus, and esophageal cancer: Scientific review. *JAMA*. 2002;287(15):1972-1981.
10. Grunow JE, al-Hafidh A, Tunell WP. Gastroesophageal reflux following percutaneous endoscopic gastrostomy in children. *J Pediatr Surg*. 1989;24(1):42-4.
11. Samuel M, Holmes K. Quantitative and qualitative analysis of gastroesophageal reflux after percutaneous endoscopic gastrostomy. *J Pediatr Surg*. 2002;37(2):256-261.
12. Wilson GJ, van der Zee DC, Bax NM. Endoscopic gastrostomy placement in the child with gastroesophageal reflux: Is concomitant antireflux surgery indicated? *J Pediatr Surg*. 2006;41(8):1441-1445.
13. Rosen R, Lord C, Nurko S. The sensitivity of multichannel intraluminal impedance and the pH probe in the evaluation of gastroesophageal reflux in children. *Clin Gastroenterol Hepatol*. 2006;4(2):167-172.
14. Skopnik H, Silny J, Heiber O, et al. Gastroesophageal reflux in infants: Evaluation of a new intraluminal impedance technique. *J Pediatr Gastroenterol Nutr*. 1996;23(5):591-598.
15. van Wijk MP, Benninga MA, Omari TI. Role of the multichannel intraluminal impedance technique in infants and children. *J Pediatr Gastroenterol Nutr*. 2009;48(1):2-12.
16. Sifrim D, Silny J, Holloway RH, et al. Patterns of gas and liquid reflux during transient lower oesophageal sphincter relaxation: A study using intraluminal electrical impedance. *Gut*. 1999;44(1):47-54.

17. Wenzl TG, Silny J, Schenke S, et al. Gastroesophageal reflux and respiratory phenomena in infants: Status of the intraluminal impedance technique. *J Pediatr Gastroenterol Nutr.* 1999;28(4):423-428.
18. Van den Driessche ML, Veereman-Wauters GA, Ghoos Y. Development of gastric emptying in healthy infants and children and reference values for the ¹³C octanoic acid breath test. *Gastroenterology.* 2000;118(4):A392.
19. Deal L, Gold BD, Gremse DA, et al. Age-specific questionnaires distinguish GERD symptom frequency and severity in infants and young children: Development and initial validation. *J Pediatr Gastroenterol Nutr.* 2005;41(2):178-185.
20. Richter JE, Bradley LA, DeMeester TR, et al. Normal 24-hr ambulatory esophageal pH values. influence of study center, pH electrode, age, and gender. *Dig Dis Sci.* 1992;37(6):849-856.
21. Sifrim D, Castell D, Dent J, et al. Gastro-oesophageal reflux monitoring: Review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut.* 2004;53(7):1024-1031.
22. Zerbib F, des Varannes SB, Roman S, et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a belgian-french cohort of healthy subjects. *Aliment Pharmacol Ther.* 2005;22(10):1011-1021.
23. Tolone S, de Bortoli N, Savarino E, et al. Pp-6 bolus clearance time is associated with reflux severity and it is inversely correlated to baseline impedance values in adolescents with gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr.* 2015;61(4):522.
24. TNO groeicalculator voor de vijfde landelijke groeistudie. 2013 ref type: Internet communication.
25. Kawahara H, Mitani Y, Nose K, et al. Should fundoplication be added at the time of gastrostomy placement in patients who are neurologically impaired? *J Pediatr Surg.* 2010;45(12):2373-2376.
26. Rudolph CD, Mazur LJ, Liptak GS, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: Recommendations of the north american society for pediatric gastroenterology and nutrition. *J Pediatr Gastroenterol Nutr.* 2001;32 Suppl 2:S1-31.
27. Kim S, Koh H, Lee JS. Gastroesophageal reflux in neurologically impaired children: What are the risk factors? *Gut Liver.* 2017 Mar; 11(2): 232-236.
28. Burd RS, Price MR, Whalen TV. The role of protective antireflux procedures in neurologically impaired children: A decision analysis. *J Pediatr Surg.* 2002;37(3):500-506.
29. Puntis JW, Thwaites R, Abel G, et al. Children with neurological disorders do not always need fundoplication concomitant with percutaneous endoscopic gastrostomy. *Dev Med Child Neurol.* 2000;42(2):97.
30. Klauser AG, Schindlbeck NE, Muller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. *Lancet.* 1990;335(8683):205-208.
31. Estevao-Costa J, Campos M, Dias JA, et al. Delayed gastric emptying and gastroesophageal reflux: A pathophysiologic relationship. *J Pediatr Gastroenterol Nutr.* 2001;32(4):471-474.

Appendix 1. Analysis of GER symptoms – of the 25 participants in the MII-pH study and the 25 non-participants.

	Preoperative	Postoperative	
	n (%) or median (IQR)	n (%) or median (IQR)	Difference
Weight-for-height percentile ²			
Participants	30 (1.0 – 85.0)	55 (25.0 – 82.0)	5.2 (-8.3 – 18.8)
Non-participants	14 (0.6 – 84.0)	12.0 (1.0 – 70.0)	0.6 (-14.5 – 15.7)
Height-for-age percentile ²			
Participants	2.0 (0.6 – 16.0)	8.0 (0.4 – 25.0)	2.9 (-1.9 – 7.7)
Non-participants	8.0 (0.6 – 30.0)	12.0 (1.0 – 35.0)	0.6 (-11.0 – 12.1)
GER symptoms in GSQ ¹			
Participants	11 / 25 (44%)	10 / 25 (40%)	$p = 1.00$
Non-participants	10 / 25 (40%)	9 / 25 (36%)	$p = 1.00$

Legend: ¹ Fisher's exact test. ² Independent samples t-test

GER = gastroesophageal reflux; GSQ = gastroesophageal reflux symptom questionnaire; IQR interquartile range; MII = multichannel intraluminal impedance.

Appendix 2A. 24-hour MII-pH monitoring: patients with preoperative pathological reflux (n=18).

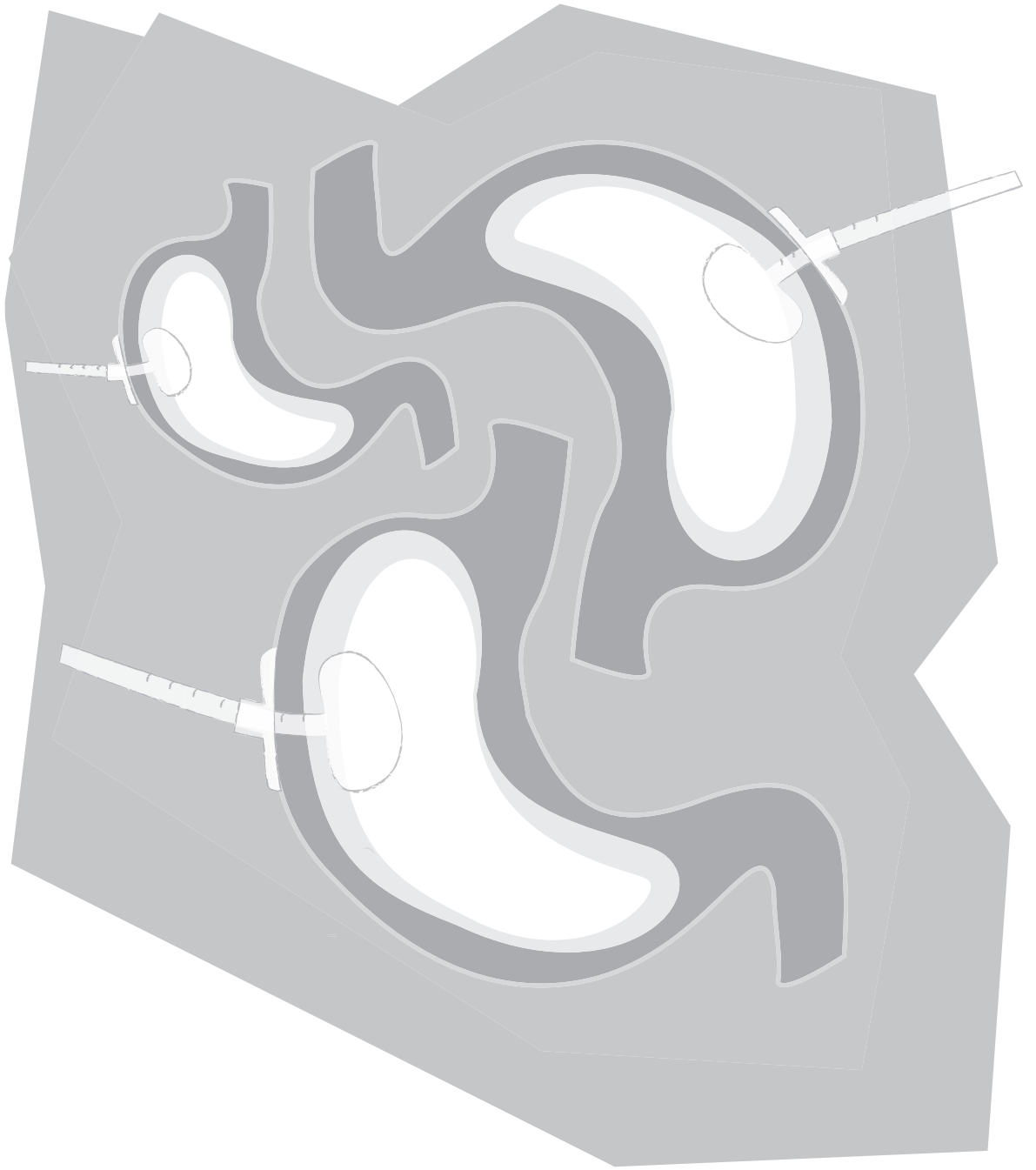
	Preoperative median (IQR)	Postoperative median (IQR)	Mean difference (95% CI) ¹
I. pH analysis			
Total acid exposure per 24 hour (%)	10.8 (5.7 – 23.1)	8.8 (3.5 – 21.7)	-1.1 (-8.3 – 6.1)
Supine position	13.3 (4.5 – 24.8)	6.1 (3.1 -19.8)	-3.1 (-9.9 – 3.6)
Upright position	11.3 (3.5 – 20.6)	9.9 (1.5 – 14.6)	-1.4 (-6.5 – 3.7)
Number of reflux episodes (pH<4)	59.9 (49.8 – 78.3)	50.0 (31.5 – 72.7)	-16.1 (-49.8 – 17.6)
Number of episodes > 5 min.	5.4 (1.5 – 25.4)	4.1 (1.2 – 11.2)	-2.0 (-5.4 – 1.4)
Longest reflux episode (min.)	33.0 (7.3 – 52.5)	17.4 (7.9 – 29.1)	-12.5 (-30.8 – 5.8)
Lowest pH	0.6 (0.5 – 1.0)	0.8 (0.5 – 1.0)	0.1 (-0.2 – 0.3)
II. Impedance analysis			
Total reflux episodes per 24 hour	73.1 (49.4 – 83.5)	75.5 (47.6 – 127.7)	14.8 (-14.1 – 43.7)
Acid	53.8 (43.3 – 70.2)	54.5 (30.6 – 74.1)	5.4 (-20.0 – 30.8)
Weakly acidic	18.1 (8.8 – 24.7)	25.1 (8.6 – 35.0)	8.0 (-1.5 – 17.6)
Liquid reflux	38.0 (28.3 – 51.2)	43.1 (32.0 – 56.0)	6.7 (-6.3 – 19.8)
Acid	28.6 (15.5 – 40.0)	23.8 (13.2 – 38.3)	4.2 (-9.8 – 18.1)
Weakly acidic	8.6 (6.4 – 20.2)	13.0 (7.1 – 23.5)	2.6 (-1.5 – 6.7)
Mixed reflux	28.0 (19.7 – 43.1)	35.2 (20.2 – 43.7)	4.6 (-12.2 – 21.4)
Acid	20.9 (16.3 – 36.9)	26.7 (8.8 – 36.2)	1.2 (-13.3 – 15.6)
Weakly acidic	6.0 (2.6 – 10.6)	10.0 (1.2 – 16.6)	4.7 (-2.5 – 12.0)
Proximal extend			
Z1 (proximal esophagus)	31.0 (12.5 – 35.0)	22.0 (16.5 – 37.0)	1.9 (-8.2 – 12.1)
Z3 (mid esophagus)	71.0 (64.5 – 83.0)	75.0 (57.5 – 87.0)	1.1 (-7.9 – 10.2)
Z5 (distal esophagus)	100 (100 – 100)	100 (100 – 100)	NA
BCT in Z6 (sec.)			
Upright	16.8 (13.8 – 20.5)	15.7 (14.5 – 17.7)	-1.3 (-5.7 – 3.1)
Supine	16.0 (12.1 – 22.1)	16.3 (10.3 – 21.5)	1.6 (-5.4 – 8.7)

Legend: 1. Paired samples t-test was used when differences were normally distributed. BCT = bolus clearance time; GER = gastroesophageal reflux; IQR = interquartile range; NA = not applicable; 95% CI = 95% confidence interval.

Appendix 2B. 24-hour MII-pH monitoring: patients without preoperative pathological reflux (n=7).

	Preoperative median (IQR)	Postoperative median (IQR)	Mean difference (95% CI) ¹
I. pH analysis			
Total acid exposure per 24 hour (%)	1.3 (0.6 – 2.6)	2.5 (1.6 – 7.5)	1.9 (0.1 – 3.8)
Supine position	0.6 (0.3 – 0.8)	2.2 (0.1 – 6.3)	3.2 (-1.5 – 8.0)
Upright position	0.6 (0.2 – 5.7)	1.9 (1.0 – 4.1)	2.3 (-3.9 – 8.6)
Number of reflux episodes (pH<4)	11.6 (6.1 – 41.2)	17.0 (8.5 – 19.2)	-7.0 (-26.2 – 12.2)
Number of episodes > 5 min.	0.0 (0.0 – 1.2)	1.3 (1.1 – 2.2)	1.3 (0.2 – 2.4)
Longest reflux episode (min.)	3.7 (2.2 – 5.7)	18.9 (6.0 – 26.2)	19.6 (-4.0 – 43.1)
Lowest pH	0.9 (0.4 – 1.4)	0.9 (0.8 – 1.1)	-0.2 (-1.3 – 0.9)
II. Impedance analysis			
Total reflux episodes per 24 hour	31.6 (23.6 – 38.8)	25.6 (17.9 – 38.2)	-4.3 (-21.0 – 12.3)
Acid	18.2 (4.1 – 25.0)	10.2 (8.1 – 21.5)	-3.8 (-14.1 – 6.4)
Weakly acidic	13.5 (6.2 – 27.5)	7.9 (5.7 – 17.1)	-0.3 (-8.8 – 8.2)
Liquid reflux	16.2 (13.7 – 19.4)	11.8 (7.9 – 21.0)	-1.3 (-9.7 – 7.1)
Acid	8.0 (1.0 – 15.0)	6.1 (3.2 – 9.0)	-1.9 (-7.1 – 3.3)
Weakly acidic	5.7 (2.1 – 14.2)	4.5 (3.9 – 8.5)	0.5 (-3.9 – 4.9)
Mixed reflux	15.0 (6.4 – 19.4)	13.9 (9.1 – 17.3)	-2.7 (-12.2 – 6.7)
Acid	6.4 (3.1 – 10.3)	5.7 (4.5 – 9.9)	-1.9 (-7.5 – 3.6)
Weakly acidic	8.0 (1.2 – 11.2)	4.5 (3.4 – 8.5)	-0.8 (-5.6 – 4.1)
Proximal extend			
Z1 (proximal esophagus)	19.0 (0.0 – 50.0)	17.0 (13.0 – 38.0)	0.71 (-23.1 – 24.5)
Z3 (mid esophagus)	55.0 (39.0 – 80.0)	74.0 (63.0 – 75.0)	12.3 (-4.7 – 29.2)
Z5 (distal esophagus)	100 (100 – 100)	100 (100 – 100)	NA
BCT in Z6 (sec.)			
Upright	17.8 (9.2 – 28.0)	12.1 (10.7 – 18.9)	3.5 (-14.3 – 21.2)
Supine	18.2 (17.3 – 34.1)	11.5 (10.3 – 20.9)	0.03 (-19.4 – 19.4)
Supine	13.2 (7.3 – 28.1)	13.4 (9.1 – 22.9)	-1.4 (-20.0 – 17.3)

Legend: 1. Paired samples *t*-test was used when differences were normally distributed. BCT = bolus clearance time; GER = gastroesophageal reflux; IQR = interquartile range; NA = not applicable; 95% CI = 95% confidence interval.



Part IV

Health-related quality of life

Chapter 6

Health-related quality of life in children after laparoscopic gastrostomy placement: a large cross-sectional study.

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ABSTRACT

Introduction: A gastrostomy placement (GP) is an established treatment to provide enteral feeding in pediatric patients with feeding difficulties aiming to improve nutritional status and health-related quality of life (HRQoL). The aim of this study was to evaluate HRQoL in children with severe feeding difficulties who have undergone GP.

Methods: A cross-sectional study was performed including 128 patients who had undergone laparoscopic GP (2004-2011). HRQoL was evaluated using the validated Pediatric Quality of Life 4.0 Inventory. Multiple regression analysis was performed to identify predictors of HRQoL.

Results: After a mean follow-up of 4.0 years (interquartile range 2.9–6.2) after GP, mean HRQoL was 53.0 out of 100 (standard deviation 21.1). HRQoL was significantly lower in children with neurologic impairment, with a mean difference of -21.4 points between neurologically impaired and neurologically normal children ($p < 0.001$). HRQoL was also lower in children with cardiac disease (-19.0 points; $p = 0.01$) and in children with a history of previous gastrointestinal surgery (-15.2 points; $p = 0.03$). Feeding through gastrojejunostomy tube (-33.0 points; $p = 0.01$) and higher age at the time of operation (-1.2 points per year; $p = 0.03$) were also associated with lower HRQoL. GP-related complications requiring reintervention were associated with lower HRQoL, although this association was not statistically significant ($p = 0.06$).

Conclusion: Children with severe feeding difficulty who have undergone GP, have significantly lower HRQoL compared to a healthy pediatric population. Neurologic impairment, cardiac disease, a history of gastrointestinal surgery, older age and the need for jejunal feeding through the gastrostomy were predictive of even lower HRQoL.

INTRODUCTION

A gastrostomy placement (GP) is an effective treatment to provide enteral tube feeding in children in need of nutritional support.^{1,2} Previous studies on GP in children have focused primarily on the physical outcomes of patients after operation.³ Health-related quality of life (HRQoL) is increasingly recognized as an essential component of patient care outcomes. It aims to assess the impact of an illness and its treatment on the dimensions of physical, psychological and social health.⁴⁻⁸ However, little is known about HRQoL as a patient care outcome in children undergoing GP, and about the factors influencing HRQoL.

The main indication for GP in children is feeding difficulty, in most cases caused by neurologic impairment (NI), cardiac disease or cystic fibrosis.⁹ In the majority of these children, HRQoL may be profoundly affected by the child's primary health condition, and can be expected to differ among various morbidities. However, other factors, such as complications related to GP (e.g. infections at the gastrostomy site, for which admission at the hospital may be indicated) or gastroesophageal reflux, may also influence the HRQoL.^{2,10}

Few studies performed in children undergoing GP have focused on HRQoL. One study investigated quality of life in children before and after GP, reporting no significant changes.¹¹ However, this study did not use validated questionnaires for quality of life assessment. A few other studies focused on the experience of parents of children undergoing GP.¹²⁻¹⁴ These studies reported a positive impact of GP on the HRQoL of parents, seen in a decrease in burden of care¹³ and an increase in self-reported social functioning, energy and general health perception.¹² These studies did not report on the HRQoL of the children themselves. To our knowledge, there is a lack of well-designed studies on the HRQoL in children undergoing GP. Where the aforementioned studies did not use validated HRQoL questionnaires, in this study the Pediatric Quality of Life (PedsQL™) 4.0 Generic Core Scales was used. This is a reliable and valid tool for proxy-report of HRQoL by caregivers and a parallel self-report for children. It has been used to assess HRQoL in healthy populations, as well as in children with numerous acute and chronic health conditions.⁵⁻⁷

Although most children have little alternative for GP, it is important to understand the population undergoing GP and the consequences of GP itself on the lives of these children. This knowledge can help physicians provide better counselling to caregivers before and after GP. The aim of our study was to evaluate HRQoL in children with severe feeding difficulty who have been treated with GP and to identify predictors (both patient characteristics and gastrostomy-related factors) of HRQoL.

METHODS

A cross-sectional study was performed including all children (age 0-18 years) who had undergone GP between January 2004 and December 2011 at the Wilhelmina Children's Hospital, University Medical Center Utrecht (UMCU).

Surgical procedure

GP was performed laparoscopically under general anesthesia in all pediatric patients. All procedures were performed or supervised by an experienced pediatric surgeon. Operations were performed by 6 different pediatric surgeons.

Ethical approval and informed consent

This study was submitted to the UMCU Ethics Committee (EC). The EC ruled that the current study did not fall under the Medical Research Involving Human Subjects Act.

Clinical assessment

Patient characteristics and medical history were derived from the electronic patient records. For evaluation of HRQoL, the PedsQL™ 4.0 Generic Core Scales was filled out. Questionnaires were given in proxy report by caregivers and completed in private.

The PedsQL™ is subdivided into four age-adjusted questionnaires (ages: 2-4; 5-7; 8-12 and 13-18 years) and a parallel self-report for children (ages: 5-7; 8-12 and 13-18 years). The inventory comprises 23 items. The HRQoL total score is divided into two main health scores: physical health summary score (8 items) and psychosocial health summary score (15 items). The psychosocial health score is reflected by the mean of three domains: emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). Items were reverse-scored and scale scores per domain were computed as the sum of the items divided by the number of items answered. Scale scores were then transformed into a scale from 0 to 100, where higher scores indicate better HRQoL. The PedsQL™ version for the age category 2-4 years is shown in **Table 1** as an illustration of HRQoL assessment.

Data on gastrostomy use and gastroesophageal reflux symptoms were obtained from the Gastroesophageal Reflux Symptom Questionnaire¹⁵ and a Gastrostomy Placement-specific questionnaire (**Table 2**). Caregivers filled out these questionnaires at the time of the HRQoL assessment.

Statistical analysis

The mean HRQoL was investigated in all subdomains of HRQoL assessment. For the PedsQL™ Generic Core Scales, no normal values are available. The only available data

as a reference for normal values are published in a large study performed by Varni *et al.* including 9500 healthy children, having a mean HRQoL score of 82.70 (\pm 15.40).¹⁶ The difference in total HRQoL between our sample size and the healthy population from Varni *et al.* was calculated using a two-sample *t*-test with Welch's correction, which is appropriate for when two samples have unequal variances and unequal sample sizes. Differences in HRQoL scores between independent samples of children (for example between NI and NN children) were calculated using the independent samples *t*-test.

To correct for incomplete data on HRQoL scores (in case caregivers did not completely fill out the questionnaire in one or multiple subdomains) we used multiple imputation to create 20 complete datasets.¹⁷ Variable groups were used to predict missing values in the imputation model.

Table 1. PedsQL™ on health-related quality of life; age category 13-18 years.

Could you tell us to what extent your teenager had trouble with each of these things in the last month? There are no right or wrong answers. Please ask for help if you have any questions.

0 if it was **never** a problem

1 if it was **almost never** a problem

2 if it was **sometimes** a problem

3 if it was **often** a problem

4 if it was **almost always** a problem

Physical functioning (having trouble with...)

Walking more than 100 metres

Running

Doing sports or other physical exercise

Heavy lifting

Taking a bath or shower independently

Having pain

Feeling tired

Emotional functioning (having trouble with...)

Feeling afraid or scared

Feeling sad

Feeling angry

Having trouble sleeping

Being worried about what might happen to him/her

Social functioning (having trouble with...)

Getting along with other teenagers

Other kids not wanting to be friends with her/him

Being bullied by other teenagers

Not being able to do things other teenagers of his/her age can do

Being able to keep up with other teenagers

Functioning at school (having trouble with...)

Paying attention in class

Forgetting things

Keeping up with work in class and doing his/her homework

Not being able to go to school because he/she is not feeling well

Not being able to go to school because he/she had to go to the doctor or hospital

Table 2. Gastrostomy Placement – specific questionnaire.

Does your child still have a gastrostomy at the moment? Yes/No
 If not, when was it removed?
 If yes, does he/she have a Mickey button or a permanent catheter?
 If yes, is he/she fed on the stomach or on the small intestine?

Did your child undergo other stomach/ small intestine/ large intestine operations?
 Date and indication for operation: ...

Did your child undergo endoscopic investigations of the stomach or small intestine?
 Date and indication for investigation: ...

How many times did your child undergo a change of the button or catheter?
 1x 2x 3x 4x 5x 5-10 >10

Did your child experience any of the following complications?
 Leakage at the gastrostomy site: daily / weekly / monthly / yearly / < yearly
 Spontaneous dislocation of the gastrostomy: 1x 2x 3x 4x 5x 5-10 >10
 Infection at the gastrostomy site: 1x 2x 3x 4x 5x 5-10 >10
 Hypergranulation at the gastrostomy site: 1x 2x 3x 4x 5x 5-10 >10
 Other complications: ...

How do you rate your satisfaction with the gastrostomy on a scale from 0-10?

Can you elaborate on the feeding schedule of your child?
 Portions scattered during the day (with pump)
 Portions scattered during the day (without pump)
 Continuous drip feeding during the night
 Continuous drip feeding during 24 hours

Did your child use any stomach enhancing medication in the last 3-4 months, for instance domperidon (Motilium) or erythromycine?
 If yes, what kind of medication?
 In which dosage?

Did your child use any antacid-inhibiting medication in the last 3-4 months, for instance omeprazole (Losec), esomeprazole (Nexium) or ranitidine (Zantac)?
 If yes, what kind of medication?
 In which dosage?

Multiple linear regression analysis was performed on the imputed data in order to identify predictors of postoperative total HRQoL. Combined results are presented. Since the sample consisted of 128 patients with complete assessment, the maximum number of independent variables entered into the regression analysis was set at 12. The variables chosen to include in the regression analysis were chosen based on univariable analysis (apart from the variables age and gender as general variables). Variables included were: age, gender, follow-up time, NI, cardiac disease, history of previous gastrointestinal surgery, acid exposure time (AET) on preoperative 24-hour pH monitoring, gastroesophageal reflux (GER) symptoms, jejunal (vs. gastric) feeding and postoperative return to the operating theatre. The influence of the independent variables in the prediction of postoperative HRQoL is represented by the

mean difference with 95% confidence intervals. Statistical analysis was performed using SPSS 22.0 statistical package (IBM, USA). Statistical significance was defined by p -values of less than 0.05.

RESULTS

Three hundred patients had undergone GP between January 2004 and December 2011. Out of these patients, 150 patients and/or their caregivers (50.0%) agreed to participate in the current study. Median follow-up time between GP and HRQoL assessment was 4.0 years (interquartile range (IQR) 2.9 – 6.2). **Figure 1** depicts an overview of patient inclusion. Out of 150 patients included, 22 caregivers of children (14.7%) did not completely fill out the PedsQL™ questionnaire in one or multiple subdomains of HRQoL.

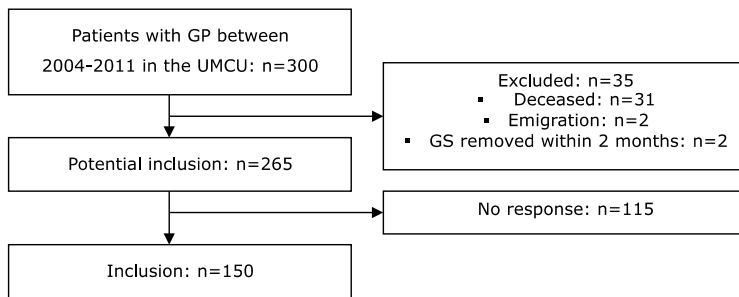


Figure 1. Flowchart of patient inclusion

Legend. GP: gastrostomy placement; UMCU University Medical Center Utrecht

Patient characteristics

Patient characteristics are described in **Table 3** for both responders and non-responders. The main underlying pathologies were NI (70.7%), cystic fibrosis (11.3%) and cardiac disease (4.7%). NI was clinically manifested as psychomotor retardation, epilepsy, microcephaly, spasticity, visual impairment and/or hypotonia.

During follow-up, 26 patients died because of causes unrelated to gastrostomy. Causes of death were deterioration of neurologic disease (n=23), cystic fibrosis (n=2) and advanced cardiac disease (n=1). These patients could consequently not be included.

Gastrostomy use and its complications.

After GP, the gastrostomy was still in place in 87% of patients. Minor gastrostomy-related complications occurred in the majority of patients (90.7%), mainly consisting of hypergranulation (60.7%), infection of the gastrostomy site (48.7%), dislodgement of the

catheter (43.3%) and obstruction of the catheter (23.3%). General satisfaction with the gastrostomy was graded as 8.2 (\pm 1.8) on a 10-point scale. After GP, some children did not tolerate feeding directly into the stomach and needed to be fed through a jejunal tube (n=4; 3.4%).

Table 3. Patient characteristics.

Demographics	Responders (n=150)	Non-responders (n=150)
Male gender (n; %)	82 (54.7%)	76 (50.7%)
Age in years at operation (median with IQR)	2.7 (1.4 – 6.1)	2.7 (1.1 – 7.6)
Elapsed time since GP in years (median with IQR)	2.9 (1.4 – 4.7)	2.0 (0.8 – 5.0)
Patient deceased	0 (0.0%)	26 (17.3%)
Gastrostomy removed	14 (9.3%)	20 (13.3%)
Indication for GP		
Neurologic impaired development (n; %)	111 (74.0%)	106 (70.7%)
Cystic fibrosis	17 (11.3%)	12 (8.0%)
Cardiac disease	4 (2.7%)	6 (4.0%)
Gastrointestinal	4 (2.7%)	5 (3.3%)
Renal disease	5 (3.3%)	2 (1.3%)
Psychiatric/ behavioral disease	3 (2.0%)	5 (3.3%)
Failure to thrive (undiagnosed)	4 (2.7%)	3 (2.0%)
Metabolic disorder	2 (1.3%)	3 (2.0%)
Dysmorphic facial features	0 (0.0%)	3 (2.0%)
Muscle disease	0 (0.0%)	2 (1.3%)
Lung disease	0 (0.0%)	2 (1.3%)
Oesophagotracheal fistula due to foreign body	0 (0.0%)	1 (0.7%)

Legend: GP: gastrostomy placement; IQR: interquartile range

Health-related quality of life (HRQoL)

After GP, the mean total HRQoL score was 53.0 out of 100 (\pm 21.1). The mean psychosocial health summary score was 62.9 (\pm 34.0) and physical health summary score was 43.4 (\pm 17.2). Between the three subdomains of psychosocial health, the children scored best in the subdomain of emotional functioning (66.9 \pm 17.5), followed by social functioning (64.9 \pm 25.0) and school functioning (57.5 \pm 24.7). These scores are all based on the observed data (n=128).

Comparing our sample with the sample of Varni *et al.*¹⁶ which we used as a reference standard (with a mean HRQoL score of 82.70 (SD 15.40)), resulted in a mean difference of 29.7 points (27.6 – 31.2).

Figure 2 shows HRQoL after GP stratified according to our main categories of morbidity. Lowest HRQoL values were found in NI children (45.8 ± 18.1), followed by children with cardiac disease (50.9 ± 23.1), cystic fibrosis (68.5 ± 15.1), behavioral disorder (72.5 ± 21.9), failure to thrive (74.5 ± 18.5) and renal disease $75.2 (\pm 18.9)$.

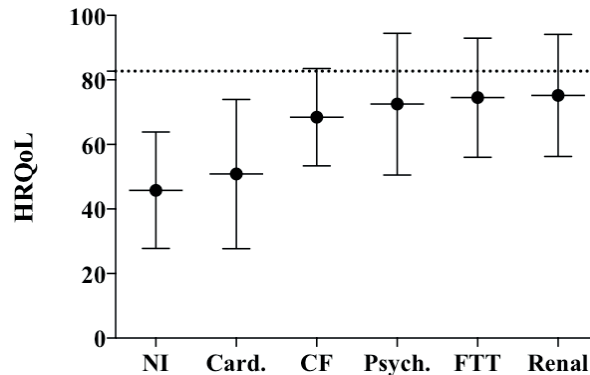


Figure 2. HRQoL stratified according to disease category.

Legend: HRQoL: Health-related quality of life. Bars are depicted in means with standard deviations. The dotted line represents the mean HRQoL of a healthy child population, as measured by Varni et al (82.70 ± 15.40). Neurologic impairment $45.8 (\pm 18.1)$; Cardiac disease $50.9 (\pm 23.1)$; Cystic fibrosis $68.5 (\pm 15.1)$; Behavioral disorder $72.5 (\pm 21.9)$; FTT Failure to thrive $74.5 (\pm 18.5)$; Renal disease $75.2 (\pm 18.9)$.

Predictors of HRQoL outcome after GP

All variables included in the multiple regression model of postoperative HRQoL and their coefficients are shown in **Table 4**. These results are based on the imputed data ($n=150$).

Patients with NI had a significantly lower postoperative HRQoL compared to the rest of the patients with normal neurodevelopment (NN), with a mean of $46.4 (\pm 18.2)$ in NI children compared to $71.4 (\pm 15.9)$ in NN children (confidence interval of the difference 23.8 – 26.5). Furthermore, NI had the highest predictive value of lower HRQoL outcome out of all variables included in the multivariable analysis, with an adjusted mean difference of 21.4 points (32.6 – 10.3) between NI and NN children. In subdomains of HRQoL, NI children scored particularly lower in the domain of physical health, with a mean physical health score of $27.5 (\pm 27.6)$ in NI children versus $71.3 (\pm 21.2)$ in NN children, with a mean difference of 43.8 points (41.8 – 45.9).

In the psychosocial domain, NI children had a smaller disadvantage compared to NN children, with a mean psychosocial health score of $56.8 (\pm 17.2)$ in NI children compared to $70.6 (\pm 15.5)$ in NN children, with a mean difference of 13.7 points (12.4 – 15.1).

Children with cardiac disease had lower HRQoL after GP, with a mean difference of -19.0 points (-32.1 – -5.9) between affected and unaffected children. In addition, children with a history of gastrointestinal surgery (mean difference of -15.2 points, (-28.2 – -1.7)) and older patients at time of operation (-1.2 points per year; (-2.3 – -0.2)) had lower HRQoL.

The need for jejunal tube feeding at the gastrostomy site was also a predictor of lower HRQoL, with a mean difference of -33.0 between children with and children without the need for jejunal tube feeding (-9.3 – -56.7).

The other variables included in the analysis did not have a statistically significant predictive value on postoperative HRQoL.

Table 4. Results of the multiple linear regression analysis of health-related quality of life after gastrostomy placement (n=150).

Predictors of health-related quality of life*	Mean difference (95% confidence interval)	p-value
Patient characteristics		
Age (years)	-1.2 (-2.3 – -0.2)	0.03
Gender (female)	-5.5 (-16.3 – 5.3)	0.32
Follow-up time (years)	-0.2 (-3.8 – 3.5)	0.93
Medical history		
Neurologic impairment	-21.4 (-32.6 – -10.3)	<0.001
Cardiac disease	-19.0 (-32.1 – -5.9)	0.01
Previous gastrointestinal surgery	-15.2 (-28.2 – -1.7)	0.03
Gastroesophageal reflux	-4.3 (-13.5 – 5.0)	0.37
Acid exposure time (%) on 24-hour pH-monitoring	-0.4 (-1.5 – 0.7)	0.48
Gastrostomy-related factors		
Jejunal feeding	-33.0 (-9.3 – -56.7)	0.01
Reinterventions in operating theater	-16.2 (-33.2 – 0.8)	0.06

Legend: * Predictors: indicating that positive predictors are correlated with better outcome in health-related quality of life.

DISCUSSION

This was the first study to investigate HRQoL in children with a gastrostomy using validated questionnaires. We found that after a mean follow-up time of 4.0 years (IQR 2.9 – 6.2), children with a gastrostomy had significantly lower HRQoL compared to the HRQoL of a large population of healthy normal children. Although it was suspected that HRQoL would be affected in this group of children, this had not previously been demonstrated.

After performing multiple regression analysis, we were able to evaluate parameters associated with lower HRQoL. NI was the main predictor of low HRQoL outcome. No data on health-related quality of life in specific comorbidities are available. However, our findings are in line with findings of another study by Varni *et al.*, reporting on HRQoL assessment in 2500 children among 33 different disease categories.¹⁶ They reported that NI children had the lowest HRQoL out of all disease categories, with a mean HRQoL of 66.85 (\pm 16.73) in their sample of 245 NI children compared to 82.70 (\pm 15.40) in their healthy sample. The mean HRQoL in our NI cohort was even lower than that of NI children in the population of Varni *et al.* This difference may be related to the severity of NI in our study population of children in need of a gastrostomy tube. However, because we do not possess the raw data of the Varni population, we cannot elaborate on this difference with any certainty.

The presence of cardiac disease was also a significant predictor of lower HRQoL after GP in our study, but to a lesser extent than NI. Other morbidity groups were not related to lower outcome in HRQoL in our study.

With respect to patient characteristics, we found that age at the time of operation was a predictor of lower HRQoL, indicating that older children undergoing GP are prone to have lower HRQoL in the long-term. The cause of this relation is unclear. A study performed by Mahant *et al.* found that children with progressive neurologic disorder had significantly lower HRQoL over time.¹¹ This may possibly explain the results in our study cohort. As expected, gender and follow-up time did not influence HRQoL.

We investigated gastrostomy-related complications and their correlation with HRQoL. In a previous study, our research group found that a large number of children experience post-GP complications. While the severity of the complications is often minor, they are nevertheless often recurrent and sometimes require reintervention in the OR.² These complications may thus have a major impact on everyday life. The impact of these complications on HRQoL of children undergoing GP had never been investigated. In our study, GP-related complications requiring reintervention in the operating theatre were negatively correlated with HRQoL. Surprisingly, this association was not statistically significant ($p=0.06$) indicating that GP-related complications may have only limited negative influence on HRQoL. Another possible explanation may lie in the long follow-up period of our study of 4.0 years (IQR 2.9 – 6.2). Since most complications occur in the first year after GP, the influence of these complications on HRQoL may diminish over time during follow-up.

A limitation of our study is that it is cross-sectional; it is therefore not possible to determine

a causal relationship between GP and HRQoL. However, with multiple regression analysis we were able to identify parameters associated with lower or higher HRQoL. The study can be a good starting point for future prospective, longitudinal studies on the influence of GP on HRQoL.

The current study provides insight into the characteristics of children with gastrostomy and the influences of patient-related characteristics and GP-related factors on their HRQoL. After GP, children have significantly lower HRQoL compared to a healthy pediatric population. Neurologic impairment, cardiac disease, a history of other gastrointestinal surgery, older age and the need for jejunal feeding through the gastrostomy were predictive of even lower HRQoL. Data on HRQoL after GP in pediatric patients is important for treating physicians when children are referred for GP, especially in providing information to patients and their caregivers.

REFERENCES

1. Corwin DS, Isaacs JS, Georgeson KE, et al. Weight and length increases in children after gastrostomy placement. *J Am Diet Assoc.* 1996;96(9):874-879.
2. Franken J, Mauritz FA, Suksamanapun N, et al. Efficacy and adverse events of laparoscopic gastrostomy placement in children: Results of a large cohort study. *Surg Endosc* 2015 Jun;29(6):1545-52.
3. Samson-Fang L, Butler C, O'Donnell M, AACPDM. Effects of gastrostomy feeding in children with cerebral palsy: An AACPDM evidence report. *Dev Med Child Neurol.* 2003;45(6):415-426.
4. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med.* 1993;118(8):622-629.
5. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: Reliability and validity of the pediatric quality of life inventory version 4.0 generic core scales in healthy and patient populations. *Med Care.* 2001;39(8):800-812.
6. Varni JW, Limbers CA. The pediatric quality of life inventory: Measuring pediatric health-related quality of life from the perspective of children and their parents. *Pediatr Clin North Am.* 2009;56(4):843-863.
7. Varni JW, Seid M, Rode CA. The PedsQL: Measurement model for the pediatric quality of life inventory. *Med Care.* 1999;37(2):126-139.
8. Varni JW, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life? An analysis of 8,591 children across age subgroups with the PedsQLTM 4.0 generic core scales. *Health Qual Life Outcomes.* 2007;5:1-7525-5-1.
9. Craig GM, Carr LJ, Cass H, et al. Medical, surgical, and health outcomes of gastrostomy feeding. *Dev Med Child Neurol.* 2006;48(5):353-360.
10. Mollitt DL, Golladay ES, Seibert JJ. Symptomatic gastroesophageal reflux following gastrostomy in neurologically impaired patients. *Pediatrics.* 1985;75(6):1124-1126.
11. Mahant S, Friedman JN, Connolly B, et al. Tube feeding and quality of life in children with severe neurological impairment. *Arch Dis Child.* 2009;94(9):668-673.
12. Sullivan PB, Juszczak E, Bachlet AM, et al. Impact of gastrostomy tube feeding on the quality of life of carers of children with cerebral palsy. *Dev Med Child Neurol.* 2004;46(12):796-800.
13. Pemberton J, Frankfurter C, Bailey K. Gastrostomy matters--the impact of pediatric surgery on caregiver quality of life. *J Pediatr Surg.* 2013; 48:963-970.
14. Thorne SE, Radford MJ, Armstrong EA. Long-term gastrostomy in children: Caregiver coping. *Gastroenterol Nurs.* 1997;20(2):46-53.
15. Deal L, Gold BD, Gremse DA, et al. Age-specific questionnaires distinguish GERD symptom frequency and severity in infants and young children: Development and initial validation. *J Pediatr Gastroenterol Nutr.* 2005;41(2):178-185.
16. Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: A comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 generic core scales. *Health Qual Life Outcomes.* 2007;5:43-7525-5-43.
17. Van Buuren S. Flexible imputation of missing data. Chapman & Hall/CRC, Boca Raton; 2012.

Chapter 7

The effect of gastrostomy placement on health-related quality of life in children: A prospective cohort study.

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ABSTRACT

Introduction: A gastrostomy placement (GP) aims to improve nutritional status and health-related quality of life (HRQoL) in children who require long-term enteral tube feeding. We evaluated the effect of GP on HRQoL.

Methods: A prospective, longitudinal cohort study was performed including patients referred for laparoscopic GP. Children and/or caregivers were asked to fill out the validated PedsQL™ questionnaire before and 3 months after surgery. The aim was to compare preoperative with postoperative HRQoL and to identify predictors of HRQoL.

Results: Fifty patients were included with a median age of 3.4 years (interquartile range 1.4-5.6). After GP, total HRQoL did not significantly increase ($p=0.30$). However, psychosocial health significantly increased: 55.8 (standard deviation ± 20.8) to 61.2 (± 19.6 ; $p=0.03$) on a 100-point scale. This was mainly due to an increase in social HRQoL: 58.2 (± 32.3) to 68.3 (± 27.9 ; $p=0.04$). HRQoL both before and after GP was significantly lower in children with neurologic impairment ($p<0.0005$). However, neurologic impairment did not influence the effect of surgery on HRQoL ($p=0.66$). Low preoperative body mass index was a predictor for improvement in HRQoL after GP.

Conclusion: After GP in children, psychosocial HRQoL improved significantly. This was mainly due to an improvement in social HRQoL.

INTRODUCTION

A gastrostomy placement (GP) is an effective treatment that provides long-term enteral tube feeding in children with feeding difficulties.^{1,2} The main indications for GP are neurologic impairment (NI), cystic fibrosis and congenital cardiac disease.^{3,4} The pediatric patients with these aforementioned conditions can suffer from poor nutritional status,⁵ which may lead to increased morbidity. Also, feeding difficulties in these patients (e.g. refusal of food or prolonged feeding time) can have a negative impact on the lives of both patients and their caregivers.⁶ GP, as a guaranteed route for enteral tube feeding, may not only lead to an improvement in nutritional status, but possibly leads to an improvement in other aspects in the lives of these patients as well, thereby increasing their health-related quality of life (HRQoL).

HRQoL is increasingly recognized as an essential part of patient care outcome. It aims to assess the impact of an illness and its treatment on the dimensions of physical and psychosocial health.⁷⁻¹⁰ To our knowledge, no study has ever prospectively evaluated the effect of GP on HRQoL. One study reported on HRQoL before and after image-guided gastrostomy or gastrojejunostomy placement in neurologically impaired children. In this study no significant changes were reported, however, this study did not use validated HRQoL questionnaires¹¹.

The lack of well-designed studies on GP and the effects of GP on its primary goal, improvement in HRQoL, led to the design of this study. Where the aforementioned study did not use validated questionnaires for HRQoL assessment, we used the Pediatric Quality of Life (PedsQL™) 4.0 generic core scales. The PedsQL™ is a validated diagnostic tool in healthy children as well as in children with numerous acute and chronic medical conditions. It has been proven to be reliable for both proxy-report by caregivers and parallel self-report for children.⁸⁻¹⁰

The primary aim of the current study is to evaluate the effect of GP on HRQoL in children prospectively. Although children in most cases have few alternatives for GP, it is important to understand the consequences of the operation on the lives of the children referred for GP, especially when providing information to caregivers. Our hypothesis is that GP in children leads to an improvement in HRQoL. We also aim to identify predictors of HRQoL and predictors of postoperative changes in HRQoL, thereby enabling us to identify the children who will gain the most benefit from GP. Finally, we investigated differences in HRQoL between self-report by patients and proxy-report by caregivers. We considered differences between proxy and self-reported HRQoL an interesting additional outcome,

because various studies on HRQoL in children indicate that information provided by caregivers does not always correspond to what children report themselves.¹²

METHODS

Study design

Between May 2012 and April 2014, a prospective, longitudinal cohort study was performed including 50 pediatric patients that underwent laparoscopic GP at the Wilhelmina Children's Hospital, University Medical Center Utrecht (UMCU). Clinical assessment was performed before GP and 3 months after operation.

Surgical procedure

GP was performed laparoscopically under general anesthesia in all pediatric patients. All procedures were performed or supervised by an experienced pediatric surgeon. Operations were performed by 6 different pediatric surgeons.

Ethical approval and trial registration

This study was part of a larger trial on GP in children, registered under the name of 'The effect of laparoscopic gastrotomy on gastric emptying: A prospective observational study in children' at the Dutch trial register (NTR3314, 29-02-2012).

Ethical approval for the study was obtained from the UMCU Ethics Committee. Prior to initiating any study procedure, informed consent was obtained from the patients' parents or caregivers and the patients themselves (when 12 years or older and without NI).

Clinical assessment

Patient characteristics and medical history were derived from the patient records. Clinical assessment included the completion of the PedsQL™. 8-10 Questionnaires were completed in proxy-report by caregivers for all children. Additionally, children without NI completed a version of the questionnaires in self-report.

The PedsQL™ is subdivided into four age-adjusted questionnaires (ages: 2-4; 5-7; 8-12 and 13-18 years) and a parallel self-report for children (ages: 5-7; 8-12 and 13-18 years). The inventory comprises 23 items. The total HRQoL score is divided into two main health scores: physical health summary score (8 items) and psychosocial health summary score (15 items), which in turn comprises the domains emotional scale score (5 items), social scale score (5 items), and functioning scale score (5 items). Scale scores per domain were computed as the sum of the items divided by the number of items answered. Items were

then reverse-scored and transformed into a scale from 0 to 100, where higher scores indicate better HRQoL.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviations for symmetric variables or as median with interquartile ranges (IQR) for skewed variables.

A linear mixed model was used to compare pre- and postoperative HRQoL and to identify predictors of HRQoL and predictors of postoperative increase or decrease in HRQoL. Mixed models are appropriate for the analysis of repeated measurements, especially in the presence of missing data on the outcome variable.¹³ Fixed effects were timing of the measurement (postoperative versus preoperative), age, neurologic impairment, cardiac disease, body mass index (BMI) and postoperative complications of GP, and a random intercept per child was included. The variables included in the mixed model were chosen based on univariate analysis. Coefficients from the mixed model represent the predictive value of the variables on the outcome variable.

To examine the effects of the examined predictors on changes in HRQoL, interactions of all variables (except for the variable 'complications', because no preoperative values of this variable were available) with timing of the measurement (preoperative versus postoperative) were added to the mixed model analysis. A significant interaction indicates that the variable is associated with postoperative change in HRQoL.

A small subsample of children was also asked to complete HRQoL questionnaires. For this subsample, the responses of children and caregivers were compared using a linear mixed model. Fixed effects were timing (postoperative versus preoperative) and children versus caregivers; a random intercept per child was included to account for clustering of measurements within children.

Statistical significance was defined by *p*-values of less than 0.05. All analyses were performed using SPSS 22.0 statistical package (IBM, USA).

RESULTS

Patient inclusion

An overview of patient inclusion is depicted in **Figure 1**. In 28 out of 31 patients that were excluded from the study the reason was the refusal of parents to participate in the clinical tests that this study was combined with, namely 24-hour pH-Impedance monitoring

studies and gastric emptying studies. Median follow-up time after GP was 4.6 months (IQR 3.7 – 5.6).

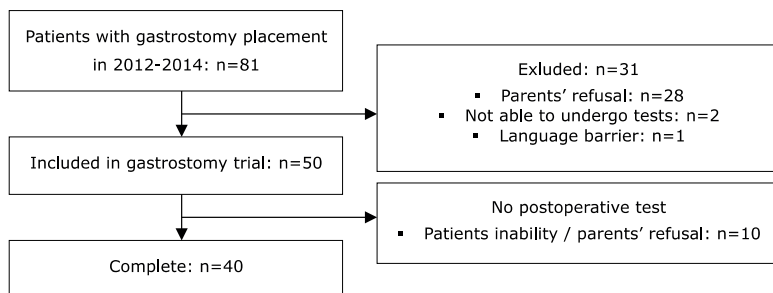


Figure 1. Flowchart of patient inclusion.

A total of 50 patients were included with a median age of 3.4 years (IQR 1.4 – 5.6). Patient characteristics are described in **Table 1**. The main underlying disease as a cause of feeding difficulty was NI (75.0%), which was clinically manifested as psychomotor retardation, epilepsy, spasticity, visual impairment and/or hypotonia. Out of 50 included patients, 10 caregivers of patients (20.0%) did not fill out the postoperative PedsQL™ questionnaire resulting in missing data on HRQoL.

Table 1. Patient characteristics (n=50).

Demographics	
	n (%)
Male gender	29 (58%)
	Median (IQR)
Age at operation	3.4 (1.4 – 5.6)
Main underlying morbidity	
Neurologic impairment	29 (58%)
Cystic fibrosis	4 (8%)
Congenital cardiac disease	2 (4%)
Undiagnosed growth retardation	2 (4%)
Pulmonary disease	2 (4%)
Short bowel disease	1 (2%)

Legend: IQR = interquartile range

Health-related quality of life after gastrostomy placement

HRQoL results before and after operation are shown in **Table 2**. These scores are based on the observed data (n=40). Although the total score and all of its subdomains increased after GP, not all changes were statistically significant. The first row of Table 2 presents the estimated change in HRQoL after GP, adjusting for all other variables in the model. After GP, there was a non-significant increase in total HRQoL score of 2.8 points on a 100-point

scale (confidence interval (CI) -2.6 – 8.3; $p=0.30$). However, analysis of subdomains of HRQoL found that, while physical health scores remained similar after operation (2.4 points; CI -1.7 – 6.3; $p=0.24$), psychosocial health scores increased significantly (5.4 points; CI 0.5 – 10.3; $p=0.03$). Further analysis of the subdomains of the psychosocial health scores found that this increase was mainly based on an increase in social scale score (10.1 points; $p=0.04$). Emotional scale score (2.8 points; $p=0.33$) and functional scale score (3.4 points; $p=0.36$) did not increase significantly compared to the preoperative values.

Table 2. Health-related quality of life in children before and after GP.

	Before GP (n = 50)	After GP (n = 40)	Difference (n=40)
Total Scale Score	54.2 ± 18.6	56.3 ± 20.5	2.1 ± 12.7
Physical Health Summary Score	45.5 ± 24.2	47.7 ± 28.0	2.1 ± 17.4
Psychosocial Health Summary Score	55.8 ± 20.8	61.2 ± 19.6	5.5 ± 15.7
Emotional Scale Score	65.4 ± 17.9	68.2 ± 19.2	2.8 ± 18.0
Social Scale Score	58.2 ± 32.3	68.3 ± 27.9	10.1 ± 24.9
Functioning Scale Score	44.2 ± 28.9	47.6 ± 26.9	3.4 ± 21.1

Legend: Data are presented as mean ± standard deviation.

Predictors of health-related quality of life.

Results of the mixed model of HRQoL are shown in **Table 3a** (in which pre- and postoperative HRQoL are analyzed in one measure). Children with NI had significantly lower total HRQoL scores compared to children without NI (coefficient -30.5, CI -19.4 – -25.3; $p<0.0005$). In analysis of subdomains of HRQoL, NI was predictive of both lower physical health scores (coefficient -43.8; CI -57.7 – -29.8; $p<0.0005$) and lower psychosocial health scores (coefficient -22.6; CI -35.4 – -9.8; $p=0.001$). Physical health scores increased with higher

Table 3a. Mixed model analysis of health-related quality of life (n=50).

	Total HRQoL score		Physical Health Summary Score		Psychosocial Health Summary Score	
	Coefficient (CI)	p-value	Coefficient (CI)	p-value	Coefficient (CI)	p-value
Postoperative (vs. preoperative)	+2.8 (-2.6 – 8.3)	0.30	+2.4 (-1.7 – 6.3)	0.24	+5.4 (0.5 – 10.3)	0.03
Age (years)	+0.9 (0.2 – 2.0)	0.09	+1.8 (0.5 – 3.2)	0.008	+0.2 (-1.0 – 1.4)	0.70
BMI (kg/m²)	-0.4 (-2.4 – 1.7)	0.73	+1.0 (-1.5 – 3.5)	0.42	-1.1 (-3.4 – 1.2)	0.34
NI (yes/no)	-30.5 (-41.6 – -19.4)	<0.0005	-43.8 (-57.7 – -29.8)	<0.001	-22.6 (-35.4 – -9.8)	0.001
Cardiac (yes/no)	-19.9 (-43.2 – 3.4)	0.09	-25.9 (-55.0 – 3.3)	0.08	-15.2 (-41.8 – 11.5)	0.26
Complication(s)	+1.3 (-2.0 – 4.7)	0.43	+1.4 (-3.0 – 5.9)	0.52	+0.7 (-3.4 – 4.8)	0.75

Legend: BMI body mass index; CI confidence interval; HRQoL health-related quality of life; NI neurologic impairment

age at the time of operation (coefficient 1.8; CI 0.5 – 3.2; $p=0.008$). The other possible parameters, BMI ($p=0.73$), cardiac disease ($p=0.09$) and complications of GP ($p=0.43$), did not predict HRQoL.

Predictors of changes in HRQoL after GP.

Results of the mixed model of changes in HRQoL after GP are shown in **Table 3b**. Analysis showed that preoperative BMI was negatively associated with a postoperative increase in total HRQoL score (coefficient -2.5 points per kg/m^2 ; CI -4.2 – -0.7; $p=0.01$). Children with lower BMI before operation showed a higher increase in postoperative HRQoL. In analysis of subdomains of HRQoL, the largest effect of BMI was found in the domain of psychosocial health (coefficient -3.8 points per kg/m^2 ; CI -5.9 – -1.7; $p=0.001$). For change in physical health scores, preoperative BMI was not a significant predictor. Age ($p=0.46$), NI ($p=0.66$) and cardiac disease ($p=0.79$) were not predictive of postoperative change in HRQoL.

Table 3b. Mixed model analysis of postoperative increase in health-related quality of life (n=50).

	Increase in total HRQoL score		Increase in Physical Health Summary Score		Increase in Psychosocial Health Summary Score	
	Coefficient (CI)	p-value	Coefficient (CI)	p-value	Coefficient (CI)	p-value
Age (years)	+0.4 (-0.6 – 1.4)	0.46	-0.2 (-1.7 – 1.2)	0.77	-0.05 (-1.2 – 1.1)	0.93
BMI (kg/m^2)	-2.5 (-4.2 – -0.7)	0.01	-2.1 (-4.7 – 0.6)	0.12	-3.8 (-5.9 – -1.7)	0.001
NI (yes/no)	+2.1 (-7.5 – 11.7)	0.66	+4.7 (-9.5 – 18.8)	0.51	+2.3 (-9.1 – 13.6)	0.69
Cardiac (yes/no)	+2.6 (-17.2 – 22.4)	0.79	+6.0 (-23.2 – 35.2)	0.68	+3.9 (-19.5 – 27.2)	0.74

Legend: BMI body mass index; CI confidence interval; HRQoL health-related quality of life; NI neurologic impairment

Differences in self-report by patients versus proxy-report by caregivers

Eleven patients were able to self-report on their HRQoL (27.5%). There was no statistically significant difference between patients' self-report and caregivers' proxy-report of total HRQoL scores, although children scored their own HRQoL on average higher than their caregivers with a difference of 4.27 points ($p=0.26$).

DISCUSSION

To our knowledge, this is the first study to prospectively investigate HRQoL after GP using validated questionnaires. Consequently, comparison to other published studies is limited.

We found that children undergoing GP significantly improved in the subdomain of psychosocial HRQoL. This was mainly based on an improvement in social HRQoL. Social HRQoL comprises the ability to function as other children of the same age. Presumably, GP helps children participate in normal daily life. This is an important finding for patients, caregivers and treating physicians when children are referred for GP.

Physical and overall HRQoL, however, remained unchanged after GP. This may be explained by the fact that physical HRQoL is heavily affected by the child's primary health condition.¹⁴ The benefits of GP are therefore not sufficient to improve overall HRQoL in these patients. In our prediction model of HRQoL we found that NI was the main predictor of lower overall HRQoL, with the largest effect size for physical HRQoL. This is in line with a cross-sectional study analyzing 150 patients four years (IQR 2.9 – 6.2) after GP. The predictive value of cardiac morbidity on HRQoL did not reach statistical significance ($p=0.09$).

Physical health summary scores increased with higher age at the time of operation, indicating that children over time gain more physical well being, possibly due to natural growth or medical assistance.

In our prediction model of postoperative changes in HRQoL, we found that the only predictor of change in HRQoL was preoperative BMI: children with lower preoperative BMI showed the largest improvement in HRQoL. This is in line with our hypothesis that children with the worst feeding difficulties gained the most benefit from a gastrostomy tube. Even though NI was predictive of lower HRQoL, NI by itself did not influence the effect of GP on HRQoL.

Pediatric self-report is the standard for HRQoL measurement. However, in young children or in children with NI it can be difficult to obtain self-reports from children. Various studies on HRQoL in children indicate that caregivers' proxy-report does not always correspond to what children report themselves.¹⁵ We found that patients consistently reported higher levels of HRQoL in comparison to their caregivers, although this was not statistically significantly different. This may be attributed to a small effect size or to the small number of children who were able to self-report on their HRQoL (27.5%), which was due to the large proportion of NI children in our study population. Similar effects were found in another study in pediatric patients undergoing laparoscopic antireflux surgery, where patient's self-report of total HRQoL scores was significantly higher than parental proxy-report with small differences between both groups.^{16,17}

Because of the heterogeneity of our patient group, the results of this study can be applied to all children undergoing GP. However, a limitation of our study is that the heterogeneity

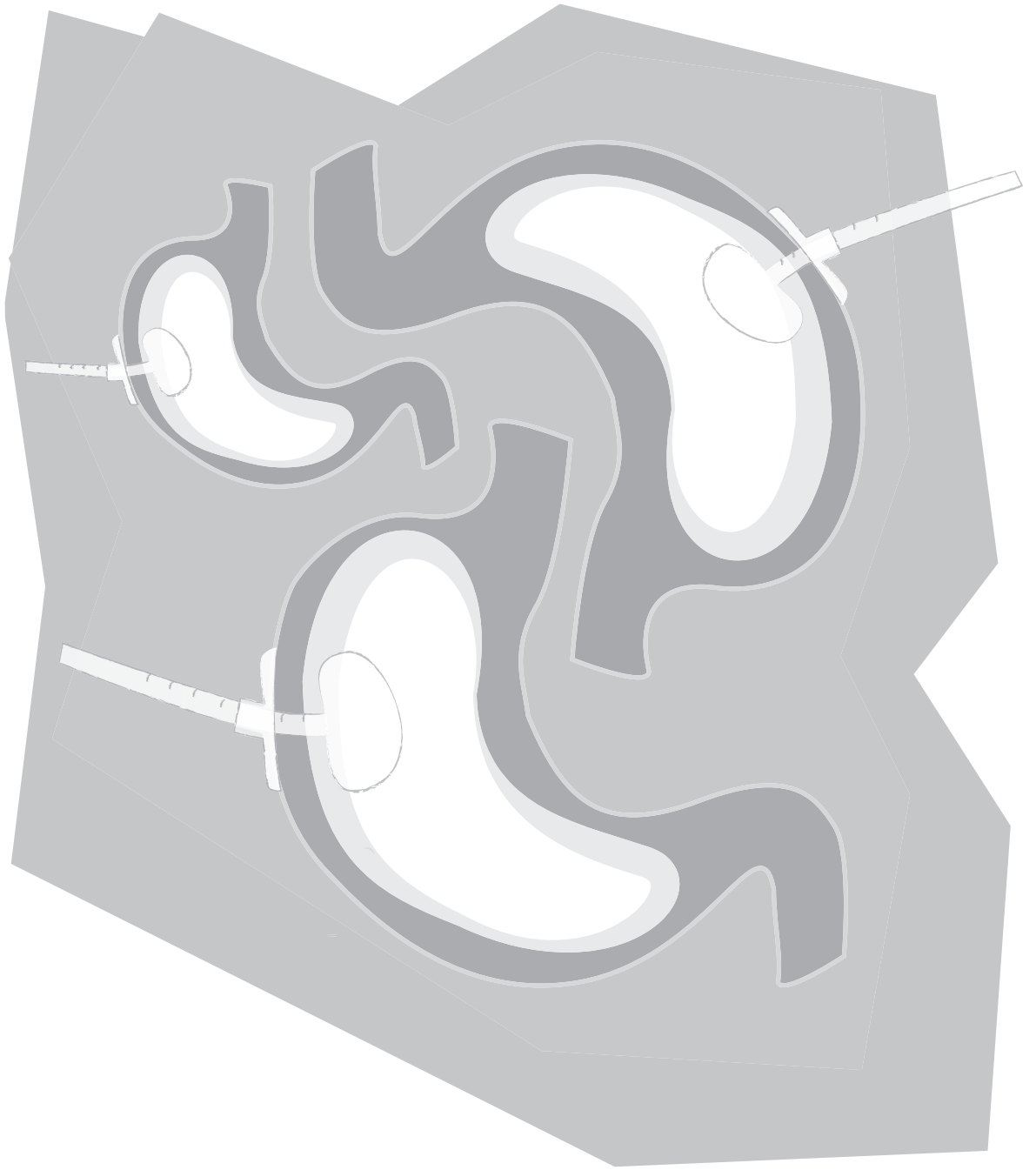
of our study population leads to variability in results and, in combination with the relatively small sample size, limits the power of our study. The inclusion of a larger patient group would have been beneficial.

In conclusion, after GP in children, psychosocial HRQoL improved significantly. This was mainly due to an improvement in social HRQoL. Presumably, GP helps children participate in normal daily life. Although children with NI had lower HRQoL (for both total HRQoL scores and all subdomains), NI by itself does not predict improvement or deterioration in HRQoL after GP. Children with low preoperative BMI gained the most benefit from GP in terms of HRQoL.

The current study adds insight in the population of pediatric patients undergoing GP and the influence of the operation on the quality of life of these patients. This knowledge can help treating physicians provide better counselling to caregivers before and after GP.

REFERENCES

1. Ferluga ED, Sathe NA, Krishnaswami S, et al. Surgical intervention for feeding and nutrition difficulties in cerebral palsy: a systematic review. *Dev Medicine & Child Neurology* 2014;56(1):31-43.
2. Craig GM, Carr LJ, Cass H, et al. Medical, surgical, and health outcomes of gastrostomy feeding. *Dev Med Child Neurol* 2006 May;48(5):353-360.
3. Srinivasan R, Irvine T, Dalzell M. Indications for percutaneous endoscopic gastrostomy and procedure-related outcome. *J Pediatr Gastroenterol Nutr* 2009 Nov;49(5):584-588.
4. Franken J, Mauritz FA, Suksamanapun N, et al. Efficacy and adverse events of laparoscopic gastrostomy placement in children: results of a large cohort study. *Surg Endosc* 29(6):1545-52.
5. Sullivan PB, Lambert B, Rose M, et al. Prevalence and severity of feeding and nutritional problems in children with neurological impairment: Oxford Feeding Study. *Dev Med Child Neurol* 2000 Oct;42(10):674-680.
6. Sullivan PB, Juszczak E, Bachlet AM, et al. Impact of gastrostomy tube feeding on the quality of life of carers of children with cerebral palsy. *Dev Med Child Neurol* 2004 Dec;46(12):796-800.
7. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med* 1993 Apr 15;118(8):622-629.
8. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001 Aug;39(8):800-812.
9. Varni JW, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life?: An analysis of 8,591 children across age subgroups with the PedsQL[®] 4.0 Generic Core Scales. *Health Qual Life Outcomes* 2007;5:1-7525-5-1.
10. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. *Med Care* 1999 Feb;37(2):126-139.
11. Mahant S, Friedman JN, Connolly B, et al. Tube feeding and quality of life in children with severe neurological impairment. *Arch Dis Child* 2009 Sep;94(9):668-673.
12. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. *Qual Life Res* 2001;10(4):347-357.
13. Hedeker D GR. Longitudinal data analysis. Hoboken: John Wiley and Sons; 2006.
14. Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales. *Health Qual Life Outcomes* 2007;5:43-7525-5-43.
15. Rajmil L, López AR, López-Aguilá S, et al. Parent-child agreement on health-related quality of life (HRQOL): a longitudinal study. *Health Qual Life Outcomes* 2013;11:101-7525-11-101.
16. Mauritz FA, Stellato RK, van Heurn LW, et al. Laparoscopic antireflux surgery increases health-related quality of life in children with GERD. *Surg Endosc* 2017 Aug;31(8):3122-3129.
17. Hanneman MJ, Sprangers MA, De Mik EL, et al. Quality of life in patients with anorectal malformation or Hirschsprung's disease: development of a disease-specific questionnaire. *Dis Colon Rectum* 2001 Nov;44(11):1650-1660.



Part V

Appendices

Chapter 8

Summary and general discussion

Gastrostomy placement (GP) is a surgical procedure frequently performed in children. A wide spectrum of pediatric patients with often severe, chronic feeding problems are referred to undergo GP. The majority of patients have severe neurologic impairment (NI).¹⁻³ Currently, GP is performed by minimally invasive techniques, either with laparoscopic GP or percutaneous endoscopic gastrostomy (PEG).⁴⁻⁶ The work presented in this thesis concerns the effects and efficacy of (laparoscopic) GP.

In **chapter one** a general introduction was written on indications for GP, different surgical procedures, and complications. Possible effects of GP on gastrointestinal function were introduced, in particular the influence of GP on gastric emptying rate and the occurrence of gastroesophageal reflux (GER). Diagnostic possibilities of these gastrointestinal functions were described. Research questions were raised and the outline of this thesis was summarized.

I. Percutaneous endoscopic versus laparoscopic gastrostomy placement

Although both the percutaneous endoscopic gastrostomy (PEG) and laparoscopic GP are nowadays widely used, controversy remains on which procedure is best practice in the pediatric population.^{7,8}

In the systematic review and meta-analysis comparing both techniques **in chapter 2** we found a lack of well-designed studies that were randomized, clearly standardized and/or of a prospective design. Five suitable retrospective studies were identified comparing 550 PEG procedures to 483 laparoscopic procedures.^{7,8} Completion rate and time to reach full feedings was similar for both procedures. PEG was associated with significantly more adjacent bowel injuries (risk ratio (RR) 5.55; $p=0.047$), early tube dislodgements (RR 7.44; $p=0.02$) and complications that required reintervention under general anesthesia (RR 2.74; $p<0.001$). In PEG, although the initial placement required less operating time, patients required a second procedure under general anesthesia for routine tube change.

These results are in favour of the laparoscopic approach. However, analysis was based on studies of a retrospective nature with heterogenic patient groups and limited data on patient selection.

II. Efficacy and adverse events

No previous studies clearly described the long-term efficacy of GP, with either weight and height values or records of long-term postoperative method of feeding. Furthermore, reported complication rates varied strongly among different studies.⁹

In **chapter 3** a large retrospective survey was described including 300 children who underwent laparoscopic GP with a median follow-up time of 2.63 years. Analysis of efficacy showed that GP was successful in providing a long-lasting route for enteral tube feeding. In 99.3% of patients GP was completed laparoscopically. Only 4.1% of patients required an alternative method of feeding after initial GP (example given a gastrojejunostomy). Nutritional status improved after GP, as weight-for-height z-scores significantly increased.

Evaluation of adverse events showed that laparoscopic GP was a relatively safe procedure, with no procedure related mortality and a major complication rate of 2.0%. However, minor complications occurred very frequently: in 221 patients (out of 300; 73.7%), a total of 408 minor complications occurred, mainly including hypergranulation, infection, leakage and dislodgement of the catheter. Forty-eight reinterventions were required, either in the operating theatre or at the radiology department.

Gastrostomy-related complications were also shortly discussed in **chapter 6**, in which questionnaires with gastrostomy-related questions were filled out by caregivers of 150 children after undergoing laparoscopic GP (in addition to health-related quality of life (HRQoL) questionnaires). Minor complications rates were comparable.

III. Gastrointestinal effects

Gastric emptying

In 15–25% of patients a gastrostomy fails, characterized by intolerance of feeding with excessive vomiting and/or leakage of gastric contents at the gastrostomy site.¹⁰ These complications might be associated with changes in gastric motility after GP. No prospective studies had been performed analyzing gastric emptying (GE) rates before and after GP.

In **chapter 4** a prospective, longitudinal cohort study was presented on 34 patients who underwent a 13C gastric emptying breath test before and 3 months after laparoscopic GP. Gastric half-emptying time significantly increased from the 57th percentile to the 79th percentile after gastrostomy ($p < 0.001$). Fifty percent of patients with normal preoperative GE (13 out of 26) developed delayed GE (>95th percentile) after GP ($p = 0.01$). The delay in GE was similar for neurologically impaired and neurologically normal children. Seventy-five percent of patients with leakage and/or feeding intolerance after GP showed delayed GE on the postoperative test. No predictors of gastrostomy failure could be identified.

Gastroesophageal reflux

The development of GER is a widely discussed complication of GP, but current evidence has been of low quality and with inconsistent results.¹¹

In **chapter 5** a prospective, longitudinal cohort was presented analyzing GER in 50 patients with symptom questionnaires and 24-hour multichannel intraluminal impedance (MII) - pH metry before and 3 months after laparoscopic GP. Twenty-five out of 50 patients successfully underwent both tests. Total acid exposure in the esophagus did not change significantly after GP: from 6.2% (3.0 – 18.1) to 6.1% (2.6 – 14.9). The number of reflux episodes did not change, neither for liquid and mixed liquid-gas reflux, nor for acid and weakly acid reflux.

The number of patients with pathological GER did not change after GP (18 out of 25 = 72%). Pathological GER dissolved after operation in some patients (n=4), while other patients developed pathological GER in the same amount (n=4). A postoperative delay in gastric emptying was correlated with an increase in total acid exposure. Low preoperative weight-for-height percentile predicted increased acid exposure after GP.

GER symptoms reported in reflux questionnaires were present in a comparable number of patients before (44%) and after GP (40%; $p = 0.73$). Symptoms were not associated with pathological GER on MII-pH analysis.

Results are in line with the large retrospective survey including 300 children in **chapter 2**, in which the incidence of GER symptoms remained unchanged: 57.8% preoperatively and 54.2% postoperatively. Antireflux surgery secondary to GP in these 300 children was indicated in only 0.7%. Sensitivity of preoperative 24-hour pH monitoring for predicting postoperative GER was only 17.5%.

These results underline the hypothesis that, overall, GP does not induce GER.

IV. Health-related quality of life

The two most important aims when placing a gastrostomy are improvement of nutritional status and improvement of HRQoL.^{12,13} No previous studies have been performed on HRQoL in children undergoing GP using validated questionnaires.

Chapter 6 offers a large prospective cross-sectional study including 126 patients who underwent laparoscopic GP. Caregivers filled out the validated PedsQL™ 4.0 generic core scales. After a median follow-up time of 4.0 years, mean HRQoL was 53.0 out of 100 (± 21.1) on a 100-point scale. For comparison: mean of a normal reference population is 82.7 (± 15.4).¹⁴ Lowest HRQoL values were found in NI children. Feeding through a gastrojejunostomy tube was predictive of lower HRQoL. Gastrostomy-related complications were not predictive of HRQoL ($p=0.06$).

In **chapter 7** a prospective, longitudinal cohort study on 50 patients is described. Caregivers filled out the PedsQL™ questionnaire before and 3 months after GP. HRQoL did not significantly increase ($p=0.30$). However, psychosocial HRQoL increased: from 55.8 (± 20.8) to 61.2 (± 19.6 ; $p=0.03$). This was mainly due to an increase in social HRQoL: 58.2 (± 32.3) to 68.3 (± 27.9 ; $p=0.04$). Worse preoperative nutritional status was a predictor for improvement in HRQoL after GP. Complications did not predict HRQoL ($p=0.43$).

Social HRQoL comprises the abilities to function as other children of the same age. Presumably, GP can help children participate in normal daily life.

General discussion and future perspectives

This thesis demonstrated that GP is successful in providing a long-lasting route for enteral tube feeding; however, GP can be associated with unanticipated diverse events.

A systematic review and meta-analysis comparing PEG and laparoscopic GP showed that the laparoscopic approach is safer since it minimizes the risk of intestinal injury. Additionally, PEG often requires repositioning of the gastrostomy tube. These findings were supported by previous studies.^{15 16} and underline the hypothesis that laparoscopic GP may be preferred over PEG. However, all analyses on this subject were based on retrospective studies. A randomized controlled trial comparing PEG with laparoscopic GP would contribute to a more widely accepted consensus on the subject.

Long-term follow-up of gastrostomy feeding showed that after laparoscopic GP, weight-for-height values increased. Previous studies on catch-up growth in children recovering from malnutrition showed that weight-for-height measures are the only reliable indicator for improvement of nutritional status, as height-for-age measures are generally more delayed during catch-up growth.^{19,20} These findings indicate that GP is an effective procedure.

Because GP is performed in children with pronounced nutritional problems and significant comorbidities, it remains difficult to determine the exact effect of GP itself on nutritional status. During interpretation of nutritional outcome, one should consider the possible confounding effects of dietary actions (such as preoperative method of feeding and the amount of nutritional intake), feeding regimen (continuous versus bolus feeding) and gastrostomy-related complications. Precise measurements of these confounders in a prospective cohort would give an even more precise estimate of the efficacy of GP.²¹ In our prospective studies (**chapters 4, 5 and 7**), in which gastrointestinal function and HRQoL were primary outcomes, the follow-up time of 3 months was too short to demonstrate weight gain and perform these analyses.

The frequently reported minor complications encountered after GP often result in increased health care utilization, significant discomfort and frequent hospital consultations.¹⁷ Indication for GP must therefore be set carefully. However, most pediatric patients undergoing GP are dependent on enteral feeding through a gastrostomy tube.¹⁸ Consultations with a specialized outpatient care unit and stoma care nurses are important for adequate treatment of leakage and infections and replacement of the catheter in case of dislodgement. In case of persisting symptoms of feeding intolerance or leakage at the gastrostomy site, timely assessment should take place for possible indication for a gastrojejunostomy, or in severe cases, for laparoscopic jejunostomy placement.

Analyzing clinical effects of GP in children, some difficulties are encountered. First, our study population is particularly **heterogeneous** with various, often co-existing, morbidities. Such patient heterogeneity can be viewed as a strength because it adds generalizability to the results and consequently, results can be applied to all patients. However, it can also lead to variability in results and, in case of small samples sizes, limit the power of the studies. Particularly in analysis of gastrointestinal function we must take into account that children may have altered gastrointestinal function because of their underlying medical conditions. The influence of GP on gastrointestinal function in the different morbidity groups might consequently differ.

Second, during the research involving clinical measurements significant **loss to follow-up** was encountered. In most cases the reason was either inability of patients to undergo the postoperative tests because of illness, or refusal by parents because they considered the tests as too much of an additional burden alongside of the fixed hospital visits. The burden of care in this vulnerable group of children makes research challenging and, at the same time, all the more necessary.

In analysis of gastric motility after GP, the cause for the postoperative delay in GE is not evident. Slow contractions of the fundus are believed to transfer gastric contents from the fundus to the antrum for trituration and subsequent GE.²² These contractions might be affected by GP in the gastric body. Motility tests such as three-dimensional ultrasonography or dynamic contrast-enhanced magnetic resonance imaging of the stomach may be useful to clarify this matter. Analysis in a larger study population is required to provide more certainty on the role of delayed GE in the occurrence of postoperative complications.

Several previous studies have stated that GP effectuates GER.¹¹ However, caution is needed when determining causality between GP and GER, because of the multifactorial pathophysiology of GER.²³ Consequently, multiple possible confounders can influence results of GER measurement. Moreover, studies were of insufficient methodological quality

and did not use MII-pH measurements.¹¹ Based on our results with MII-pH measurements in a prospective cohort (**chapter 5**), we conclude that GP was not associated with an increase in GER.

In current literature, there are conflicting reports regarding the association between delayed GE and GER, possibly due to varying methods of GE assessment.²⁴⁻²⁶ In **chapter 5**, a postoperative delay in GE was correlated with an increase in total acid exposure. This may partly explain why esophageal acid exposure increases in some of the patients after GP, while it diminishes in others. Hypothetically, delayed GE may accentuate GER by prolonging transient lower esophageal sphincter relaxations and increasing the volume of the refluxate.

Although GP does not induce GER, a large part of the children after GP do have GER, either pre-existent or newly developed.²⁷ There are several options for management of post-gastrostomy GER, highlighted by the small percentage of patients who later required antireflux surgery in our long-term follow-up study (**chapter 3**). These results justify that routine fundoplication in present day is no longer used as a standard procedure in children with preoperative pathological GER undergoing GP. Furthermore, routine 24-hour pH monitoring before GP does not result in a reliable prognostic value for the development of postoperative GER and is therefore no longer required in routine preoperative workup.

HRQoL plays a particularly essential role in the pediatric population undergoing GP, a heavily affected group of children. In this thesis patients improved mainly in the social domain of HRQoL while overall HRQoL did not change. These patient reported outcomes are not easily translated towards improvements in our daily practice. They can, however, be an indication of 'how well we do'. Additionally, these data can be helpful for treating physicians in providing information towards parents when children are referred for GP.

Conclusion

In conclusion, in children who are dependent on a gastrostomy tube for enteral feeding, GP is an efficient way of providing weight gain in the long term. Laparoscopic GP carries a lower risk of major complications and reoperations compared to the percutaneous endoscopic technique. GP may increase the child's social HRQoL. The possibility that GP causes delayed GE should be recognized by pediatric surgeons, even though the exact mechanism of this relation remains to be clarified. In contrast to previous reports, GP did not cause gastroesophageal reflux. In some children, gastrostomy fails, characterized by feeding intolerance and recurring minor complications with the gastrostomy tube. Therefore, consultations with specialized outpatient care units are important for adequate

guidance of patients and caregivers. In the majority of patients, the benefits of GP way heavier than the potential side effects of GP.

REFERENCES

1. Fortunato J CC. Outcomes of percutaneous endoscopic gastrostomy in children. *Curr Gastroenterol Rep* 2011;13(3):293-9.
2. Khattak IU, Kimber C, Kiely EM, et al. Percutaneous endoscopic gastrostomy in paediatric practice: Complications and outcome. *J Pediatr Surg*. 1998;33(1):67-72.
3. Srinivasan R, Irvine T, Dalzell M. Indications for percutaneous endoscopic gastrostomy and procedure-related outcome. *J Pediatr Gastroenterol Nutr*. 2009;49(5):584-588.
4. Gauderer MW, Ponsky JL, Izant RJ Jr. Gastrostomy without laparotomy: A percutaneous endoscopic technique. *J Pediatr Surg*. 1980;15(6):872-875.
5. Georgeson KE. Laparoscopic gastrostomy and fundoplication. *Pediatr Ann*. 1993;22(11):675-677.
6. Collins JB 3rd, Georgeson KE, Vicente Y, et al. Comparison of open and laparoscopic gastrostomy and fundoplication in 120 patients. *J Pediatr Surg*. 1995;30(7):1065-70.
7. Akay B, Capizzani TR, Lee AM, et al. Gastrostomy tube placement in infants and children: Is there a preferred technique? *J Pediatr Surg*. 2010;45(6):1147-1152.
8. Zamakhshary M, Jamal M, Blair GK, et al. Laparoscopic vs percutaneous endoscopic gastrostomy tube insertion: A new pediatric gold standard? *J Pediatr Surg*. 2005;40(5):859-862.
9. Samson-Fang L, Butler C, O'Donnell M, AACPDM. Effects of gastrostomy feeding in children with cerebral palsy: An AACPDM evidence report. *Dev Med Child Neurol*. 2003;45(6):415-426.
10. Friedman JN, Ahmed S, Connolly B, et al. Complications associated with image-guided gastrostomy and gastrojejunostomy tubes in children. *Pediatrics*. 2004;114(2):458-461.
11. Noble LJ, Dalzell AM, El-Matary W. The relationship between percutaneous endoscopic gastrostomy and gastro-oesophageal reflux disease in children: A systematic review. *Surg Endosc*. 2012;26(9):2504-2512.
12. Rempel GR, Colwell SO, Nelson RP. Growth in children with cerebral palsy fed via gastrostomy. *Pediatrics*. 1988;82(6):857-862.
13. Corwin DS, Isaacs JS, Georgeson KE, et al. Weight and length increases in children after gastrostomy placement. *J Am Diet Assoc*. 1996;96(9):874-879.
14. Varni JW, Burwinkle TM, Seid M. The PedsQL 4.0 as a school population health measure: Feasibility, reliability, and validity. *Qual Life Res*. 2006;15(2):203-215.
15. Baker L, Beres AL, Baird R. A systematic review and meta-analysis of gastrostomy insertion techniques in children. *J Pediatr Surg*. 2015;50(5):718-725.
16. Petrosyan M, Khalafallah AM, Franklin AL, et al. Laparoscopic gastrostomy is superior to percutaneous endoscopic gastrostomy tube placement in children less than 5 years of age. *J Laparoendosc Adv Surg Tech A*. 2016;26(7):570-573.
17. Crosby J, Duerksen D. A retrospective survey of tube-related complications in patients receiving long-term home enteral nutrition. *Dig Dis Sci*. 2005;50(9):1712-1717.
18. Srinivasan R, Irvine T, Dalzell M. Indications for percutaneous endoscopic gastrostomy and procedure-related outcome. *J Pediatr Gastroenterol Nutr*. 2009;49(5):584-588.
19. Kang A, Zamora SA, Scott RB, et al. Catch-up growth in children treated with home enteral nutrition. *Pediatrics*. 1998;102(4 Pt 1):951-955.
20. Walker SP, Golden MH. Growth in length of children recovering from severe malnutrition. *Eur J Clin Nutr*. 1988;42(5):395-404.
21. Sullivan PB, Juszczak E, Bachlet AM, et al. Gastrostomy tube feeding in children with cerebral palsy: A prospective, longitudinal study. *Dev Med Child Neurol*. 2005;47(2):77-85.

22. Nguyen NQ, Fraser RJ, Bryant LK, et al. Functional association between proximal and distal gastric motility during fasting and duodenal nutrient stimulation in humans. *Neurogastroenterol Motil.* 2007;19(8):638-645.
23. Kawahara H, Dent J, Davidson G. Mechanisms responsible for gastroesophageal reflux in children. *Gastroenterology.* 1997;113(2):399-408.
24. Knatten CK, Avitsland TL, Medhus AW, et al. Gastric emptying in children with gastroesophageal reflux and in healthy children. *J Pediatr Surg.* 2013;48(9):1856-1861.
25. Kawahara H, Tazuke Y, Soh H, et al. Does laparoscopy-aided gastrostomy placement improve or worsen gastroesophageal reflux in patients with neurological impairment? *J Pediatr Surg.* 2014;49(12):1742-1745.
26. Sager S, Halac M, Selcuk N, et al. Temporal relationship between gastroesophageal reflux and rate of gastric emptying in children. *Nucl Med Commun.* 2010;31(12):1059-1062.
27. Kim S, Koh H, Lee JS. Gastroesophageal reflux in neurologically impaired children: What are the risk factors? *Gut Liver.* 2017 Mar; 11(2): 232–236.

Chapter 9

**Nederlandse samenvatting en
algemene discussie**

Gastrostomie (oftewel het plaatsen van een gastrostoma) is een chirurgische procedure die frequent uitgevoerd wordt in pediatrie patiënten. Een breed spectrum aan pediatrie patiënten met doorgaans ernstige, chronische voedingsproblemen wordt voor gastrostomie verwezen. De meerderheid van deze patiënten leidt aan aangeboren neurologische aandoeningen.¹⁻³ Gastrostomie wordt tegenwoordig uitgevoerd via minimaal invasieve procedures, namelijk door middel van laparoscopische gastrostomie of percutaan endoscopische gastrostomie (PEG).⁴⁻⁶ Dit proefschrift beschreef de effectiviteit en bijkomende effecten van (hoofdzakelijk laparoscopische) gastrostomie.

In **hoofdstuk 1** werd een algemene introductie gegeven waarbij aan bod kwamen: indicaties voor gastrostomie, de verschillende chirurgische procedures en mogelijke complicaties van de operatie. Mogelijke effecten van gastrostomie op het gastro-intestinale stelsel werden geïntroduceerd, zoals de invloed van gastrostomie op de maaglediging en op het optreden van gastro-oesofageale reflux (GOR). De diagnostische mogelijkheden voor het meten van deze gastro-intestinale fenomenen werden beschreven. De onderzoeksvragen en hoofdlijnen van dit proefschrift werden opgesteld.

I. Percutaan endoscopische versus laparoscopische gastrostomie

Ondanks dat PEG en laparoscopische gastrostomie (LG) tegenwoordig beide alom uitgevoerd worden, blijft er controverse bestaan over welke procedure de voorkeur heeft voor de pediatrie populatie.^{7,8}

In de systematische review en meta-analyse **in chapter 2** werden beide technieken met elkaar vergeleken. Hierbij werd een gebrek gevonden aan goed opgezette studies met een randomisatie, een duidelijke standaardisatie en/of met een prospectieve studie-opzet. Vijf geschikte retrospectieve studies werden geïdentificeerd waarin 550 PEG procedures en 483 LG procedures met elkaar werden vergeleken.^{7,8} Het voltooiingspercentage en de tijd tot het bereiken van volledige voeding via het gastrostoma waren gelijk voor beide procedures. PEG was geassocieerd met een significant groter aantal letsels aan omliggende darmen (risk ratio (RR) 5.55; $p=0.047$), vroege losrakingen van de catheter (RR 7.44; $p=0.02$) en complicaties waarvoor reïnterventie onder algehele anesthesie geïndiceerd was (RR 2.74; $p<0.001$). Alhoewel er bij patiënten die PEG ondergingen sprake was van een kortere operatieduur van de initiële procedure, was er bij deze patiënten een tweede procedure nodig onder algehele anesthesie voor de routinematige wissel van de catheter.

Deze resultaten spreken in het voordeel van de laparoscopische benadering. Echter, het is belangrijk hierbij rekening te houden met het feit dat de meta-analyse enkel gebaseerd was op studies met een retrospectieve studie-opzet en er sprake was van heterogene patiëntengroepen en gelimiteerde data over de patiëntenselectie.

II. Werkzaamheid en nadelige gevolgen

Geen eerdere studies hebben duidelijk de werkzaamheid van gastrostomie op de lange termijn beschreven, met gewicht- en lengtematen of documentatie van de manier van voeden na een lange duur na operatie. Daarnaast is er sprake van een sterke variatie in de complicatiepercentages van de verschillende studies.⁹

In **hoofdstuk 3** werd een grote retrospectieve studie beschreven met 300 kinderen die LG hadden ondergaan met een mediane opvolgtijd van 2.63 jaar. Het analyseren van de werkzaamheid van LG in deze kinderen toonde dat de operatie succesvol was in het verschaffen van een langdurige route voor het geven van enterale voeding. In 99.3% van de patiënten werd de ingreep laparoscopisch voltooid. In slechts 4.1% van de patiënten was na de initiële ingreep tijdens de opvolgtijd een alternatieve route nodig voor het geven van voeding, zoals een gastrojejunostomie. De voedingsstatus van patiënten verbeterde na LG, wat te zien was aan het feit dat gewicht-voor-lengte z-scores significant toenamen.

De evaluatie van de nadelige gevolgen van LG toonde dat de procedure relatief veilig is, met afwezigheid van procedure-gerelateerde mortaliteit en een percentage ernstige (vaak peroperatieve) complicaties van 2.0%. Daarentegen vonden minder ernstige 'minor' complicaties (vaak postoperatief) zeer frequent plaats: in 221 patiënten (van de 300; 73.7%) traden 408 minor complicaties op, voornamelijk bestaand uit hypergranulatie, infectie of lekkage van maaginhoud rond de gastrostoma-insteek of loslating van de catheter. Er waren 48 reïnterventies geïndiceerd die plaatsvonden ofwel in de operatiekamer ofwel op de radiologie-afdeling.

Complicaties gerelateerd aan LG werden ook kort beschreven in **hoofdstuk 6**, waar lijsten met vragen omtrent het gastrostoma werden ingevuld door verzorgers van 150 kinderen die LG hadden ondergaan (in aanvulling op vragen met betrekking tot kwaliteit van leven). De percentages van minor complicaties in deze studie waren vergelijkbaar met die uit **hoofdstuk 3**.

III. Gastro-intestinale effecten

Maaglediging

In 15 tot 25 procent van de patiënten faalt een gastrostomie, wat gekenmerkt wordt door intolerantie voor voeding, excessief spugen en/of lekkage van maaginhoud langs de gastrostoma-insteek.¹⁰ Dit falen zou geassocieerd kunnen zijn met veranderingen in maaglediging na operatie. Er zijn tot dusver geen prospectieve studies uitgevoerd die de maagledigingsnelheid onderzochten voor en na LG.

In **hoofdstuk 4** werd een prospectieve, longitudinale cohortstudie gepresenteerd met 34 patiënten die een ¹³C Octanoaat-ademtest ondergingen voor en 3 maanden na LG. De halfwaardetijd van maaglediging nam significant toe vanaf het 57e percentiel preoperatief naar het 79e percentiel postoperatief ($p < 0.001$). Vijftig procent van de patiënten met een preoperatief normale maaglediging (13 van de 26) ontwikkelde een vertraagde maaglediging (>95e percentiel) na operatie ($p = 0.01$). De vertraging in maaglediging was gelijk voor de neurologische aangedane kinderen en de overige groep patiënten. Van de patiënten met lekkage en/of intolerantie voor voeding na de operatie had 75 procent een vertraagde maaglediging op de postoperatieve test. Er konden geen predictoren van falen van het gastrostoma geïdentificeerd worden.

Gastro-oesofageale reflux

Het ontwikkelen van GOR is een veel besproken mogelijke complicatie van LG, maar verrichte onderzoeken zijn overwegend van lage kwaliteit en tonen inconsistente resultaten.¹¹

In **hoofdstuk 5** werd een prospectieve, longitudinale cohortstudie gepresenteerd waarin 50 patiënten geanalyseerd werden door middel van GOR symptoomvragenlijsten en 24-uurs multikanaals intraluminaal impedantie (MII) – pH metingen zowel voor als 3 maanden na LG. Vijfentwintig van de 50 patiënten ondergingen succesvol beide testen. De totale zuurexpositie in de oesofagus maakte geen significante verandering door: van 6.2% (3.0 – 18.1) naar 6.1% (2.6 – 14.9). Het aantal refluxepisoden veranderde niet; dit gold voor de vloeibare en vloeibaar-gas gemengde reflux, en ook voor de zure en de zwak-zure reflux.

Het aantal patiënten met pathologische GOR veranderde niet significant na operatie (72% zowel voor als na operatie). Pathologische GOR verdween postoperatief in een paar patiënten ($n = 4$) en een gelijk aantal patiënten ($n = 4$) ontwikkelde juist pathologische GOR. Een vertraging in maaglediging na operatie was gecorreleerd aan de totale zuurexpositie in de oesofagus ($r_s 0.49$ $p = 0.03$). Een laag preoperatief gewicht-voor-lengte percentiel was voorspellend voor een toename in zuurexpositie na LG met een voorspellende waarde (B) van -0.5 (-0.28 - -0.1).

In de symptoomvragenlijsten waren GOR symptomen aanwezig in een vergelijkbaar aantal patiënten voor (44%) en na LG (40%; $p = 0.73$). Symptomen waren niet gecorreleerd aan pathologische GOR op de MII-pH analyse.

Resultaten komen overeen met de resultaten uit de retrospectieve studie van **hoofdstuk 2**, waar de incidentie van GOR symptomen in de 300 kinderen onveranderd bleef: 57.8% voor operatie en 54.2% na operatie. Tijdens de vervolgtijd waren antirefluxoperaties secundair aan LG geïndiceerd in slechts 0.7% van deze 300 kinderen. De sensitiviteit van

preoperatieve 24-uurs pH monitoring voor het voorspellen van postoperatieve GOR was tevens slechts 17.5%.

De resultaten ondersteunden de hypothese dat LG in het algemeen geen GOR veroorzaakt.

IV. Gezondheidsgerelateerde kwaliteit van leven

De twee belangrijkste doelen van een gastrostomie zijn verbetering van voedingsstatus en gezondheidsgerelateerde kwaliteit van leven (GKvL).^{12,13} Er zijn niet eerder studies verricht naar GKvL in kinderen die LG ondergingen waarbij gebruik gemaakt werd van gevalideerde vragenlijsten.

In **hoofdstuk 6** werd een grote cross-sectionele studie beschreven van 126 patiënten die LG hadden ondergaan. Verzorgers vulden de 'PedsQL™ 4.0 generic core scales' in, een gevalideerde vragenlijst voor de evaluatie van GKvL in kinderen. Na een mediane vervolgdur van 4.0 jaren na de operatie was de gemiddelde GKvL 53.0 op een schaal van 100 (\pm 21.1). De laagste GKvL waarden werden aangetroffen in de kinderen met neurologische aandoeningen. De noodzaak tot het voeden door een gastrojejunostomie was voorspellend voor een lagere GKvL. Complicaties gerelateerd aan LG waren niet voorspellend voor GKvL ($p = 0.06$).

In **hoofdstuk 7** werd een prospectieve, longitudinale cohortstudie beschreven van 50 patiënten. Verzorgers vulden de 'PedsQL™ 4.0 generic core scales' in voor en 3 maanden na LG. De totale GKvL veranderde na operatie niet ($p = 0.30$). Echter, de psychosociale GKvL nam wel toe: van 55.8 (\pm 20.8) naar 61.2 (\pm 19.6); ($p = 0.03$). Dit werd met name veroorzaakt door een toename in de sociale GKvL: 58.2 (\pm 32.3) naar 68.3 (\pm 27.9; $p = 0.04$). Slechte preoperatieve voedingsstatus was een voorspeller van verbetering in GKvL na LG. Complicaties waren niet voorspellend voor GKvL ($p = 0.43$).

Sociale GKvL representeert de mogelijkheid om te functioneren zoals kinderen van dezelfde leeftijd. Vermoedelijk worden patiënten door LG geholpen om in het normale dagelijkse leven te participeren.

Algemene discussie

Dit proefschrift toonde aan dat gastrostomie een effectieve procedure is voor het geven van enterale voeding op de lange termijn. Echter, gastrostomie kan ook gepaard gaan met nadelige gevolgen.

De systematische review en meta-analyse waarin PEG en LG werden vergeleken vond dat de laparoscopische benadering veiliger is omdat deze procedure gepaard gaat met een lager risico op letsel aan de darmen. Daarnaast is bij PEG doorgaans een tweede procedure nodig voor het herpositioneren van het gastrostoma. Overige studies ondersteunen deze resultaten.^{15,16} De bevindingen ondersteunen de hypothese dat LG verkozen mag worden boven PEG. De analyses waren echter wel gebaseerd op retrospectieve studies. Een gerandomiseerde vergelijkende studie tussen beide entiteiten kan bijdragen aan een meer wijd geaccepteerde consensus.

Bij de analyse van voedingsstatus op de lange termijn na LG werd een toename van gewicht-voor-lengte maten gevonden. Eerdere studies betreffende inhaalgroei in kinderen die herstelden van malnutritie toonden dat gewicht-voor-lengte percentielen de enige betrouwbare indicator zijn van verbetering van voedingsstatus, aangezien lengte-voor-leeftijd percentielen doorgaans meer achterlopen tijdens inhaalgroei.^{17,18} Onze studieresultaten wijzen erop dat LG een effectieve procedure is. Doordat LG wordt verricht in kinderen met uitgesproken voedingsproblemen en aanzienlijke morbiditeit blijft het moeilijk om met zekerheid het precieze causale effect van LG op de voedingsstatus vast te stellen. Bij het interpreteren van voedingsstatus moet men rekening houden met factoren die als confounders kunnen optreden, zoals dieet (bijv. de preoperatieve manier van voeden en de hoeveelheid voedingsinname), het voedingsschema via het gastrostoma (continue versus bolusvoeding) en complicaties gerelateerd aan de gastrostomie. Precieze metingen van deze confounders in een prospectief cohort kan een nog beter oordeel geven van de werkzaamheid van LG.¹⁹ In onze prospectieve studies (**hoofdstukken 4, 5 en 7**) die gericht waren op het analyseren van gastro-intestinale functie en GKvL, was de vervolgtijd van 3 maanden te kort om veranderingen in voedingstoestand te meten en deze analyses te kunnen verrichten.

De frequent optredende 'minor' complicaties na LG resulteren in verhoogd gebruik van de gezondheidszorg, discomfort bij patiënten en ouders en frequente ziekenhuisbezoeken.²⁰ De indicatie voor gastrostomie moet om deze reden zorgvuldig gesteld worden. De meeste pediatrische patiënten die gastrostomie ondergaan zijn echter afhankelijk van enterale voeding.³ Consultaties met een gespecialiseerde polikliniek en stomaverpleegkundigen zijn belangrijk voor adequate behandeling van hypergranulatie, lekkage en infectie en het tijdig herplaatsen van de catheter in het geval van losraking. In het geval van

ernstige symptomen van intolerantie voor voeding over het gastrostoma of lekkage van maaginhoud, is tijdige beoordeling belangrijk voor het eventueel stellen van de indicatie voor een gastrojejunostomie of, in ernstige gevallen, voor een laparoscopisch geplaatste jejunostomie.

Bij het onderzoeken van de klinische gevolgen van LG in kinderen stuit men op enkele moeilijkheden. Ten eerste is onze studiepopulatie bijzonder heterogeen met een sterke variatie aan vaak samen voorkomende morbiditeiten. Deze heterogeniteit kan worden gezien als een sterkte, omdat het generaliseerbaarheid aan de resultaten geeft waardoor resultaten op alle patiënten van toepassing kunnen zijn. Het kan echter ook leiden tot te grote variabiliteit in de resultaten en in het geval van kleine onderzoeksgroepen de power van de studies beperken. In het bijzonder bij het analyseren van gastro-intestinale functies moeten we rekening houden met het feit dat kinderen in onze onderzoeksgroep reeds een veranderde gastro-intestinale functie hebben ten gevolge van hun onderliggende morbiditeit. Derhalve kan de invloed van LG op deze functie in de verschillende groepen van morbiditeit mogelijk verschillen.

Ten tweede zijn er bij het onderzoek met klinische metingen een aanzienlijk aantal patiënten verloren voor follow-up. In de meeste gevallen kwam dit door het overmogen van patiënten om de postoperatieve testen te ondergaan vanwege ziekte of door het weigeren van ouders doordat zij de testen als een te grote last ervaarden naast de vaste ziekenhuisbezoeken voor hun kind. De last van de zorg in deze kwetsbare groep kinderen maakt onderzoek uitdagend, maar tegelijkertijd des te meer noodzakelijk.

Bij het analyseren van de maaglediging na LG is de oorzaak van de postoperatieve vertraging niet evident. Er wordt gedacht dat trage contracties van de fundus de maaginhoud van de fundus naar het antrum transporteren voor het vermalen van de inhoud en vervolgens ledigen van de maag.²¹ Deze contracties zouden aangetast kunnen worden door gastrostomie in de maag. Het onderzoeken van de motiliteit van de maag, met bijvoorbeeld driedimensionale echo of dynamische contrast-versterkte magnetische resonantie imaging (MRI), kan zinvol zijn om deze vraag te onderzoeken. Tevens is analyse in grotere studiepopulaties nodig om meer zekerheid te bieden over de rol van vertraagde maaglediging in het optreden van postoperatieve complicaties.

Meerdere voorgaande studies hebben gesteld dat gastrostomie GOR veroorzaakt.¹¹ Echter, het is belangrijk voorzichtig te zijn bij het benoemen van causaliteit tussen gastrostomie en GOR, vanwege de multifactoriële pathofysiologie van GOR.²² Derhalve kunnen diverse confounders invloed hebben op de resultaten van GOR metingen. Daarnaast waren studies grotendeels van onvoldoende methodologische kwaliteit en maakten zij geen gebruik van

MII-pH metingen.¹¹ Gebaseerd op onze resultaten met MII-pH metingen in een prospectief cohort (**hoofdstuk 5**) konden we concluderen dat gastrostomie niet tot een toename van GOR leidde.

In de huidige literatuur zijn er tegenstrijdige resultaten gerapporteerd over de associatie tussen maaglediging en GOR, wat deels veroorzaakt zou kunnen worden door de sterke variatie in de meetmethoden van zowel maaglediging als GOR.²³⁻²⁵ In dit proefschrift was een postoperatieve vertraging in maaglediging gecorreleerd aan een toename van zuurexpositie in de oesofagus (**hoofdstuk 5**). Dit zou kunnen verklaren waarom de zuurexpositie in sommige patiënten na LG toeneemt, terwijl het in anderen afneemt.

Alhoewel LG geen GOR veroorzaakt, heeft wel een groot deel van de patiënten in onze populatie GOR, ofwel pre-existent ofwel nieuw ontwikkeld.²⁶ Er zijn verschillende opties voor de behandeling van GOR in kinderen met een gastrostoma. In de lange termijn vervolgstudie werd er maar een klein percentage patiënten gevonden dat antirefluxchirurgie nodig had in de jaren na de gastrostomie (**hoofdstuk 3**). Deze resultaten verdedigen het feit dat er tegenwoordig niet langer routinematig een funduplicatie wordt verricht tegelijk met LG in kinderen met preoperatief pathologische GOR. Verder is routinematige 24-uurs pH meting voorafgaand aan LG niet voorspellend voor het ontwikkelen van postoperatieve GOR en hoeft daardoor niet langer te worden verricht in de standaard preoperatieve procedure.

GKvL speelt een bijzonder essentiële rol in de populatie van pediatrische patiënten die gastrostomie ondergaat, omdat het een zwaar aangedane groep kinderen betreft. In dit proefschrift verbeterden patiënten drie maanden na operatie voornamelijk in het sociale domein van GKvL, terwijl de algehele GKvL niet significant toenam. Deze patiënt-gerelateerde uitkomsten zijn niet gemakkelijk te vertalen naar onze dagelijkse praktijk. Ze kunnen echter wel een indicatie zijn van 'hoe goed we handelen'. Daarnaast kunnen deze resultaten nuttig zijn voor behandelaren bij het geven van informatie aan ouders wanneer kinderen voor gastrostomie worden verwezen.

Conclusie

Concluderend is gastrostomie een effectieve manier om verbetering van voedingsstatus op de lange termijn te bereiken voor kinderen die afhankelijk zijn van enterale voeding. Laparoscopische gastrostomie lijkt een lager risico te geven op ernstige complicaties en reoperaties in vergelijking met de percutane endoscopische benadering. Gastrostomie kan de sociale GKvL van kinderen verbeteren. De kinderchirurg dient rekening te houden met de mogelijkheid dat gastrostomie tot een vertraagde maaglediging kan leiden, ondanks dat het precieze mechanisme en de gevolgen hiervan nog opgehelderd moeten worden. In

tegenstelling tot sommige eerdere publicaties leidt gastrostomie niet tot gastro-oesofageale reflux. In sommige kinderen faalt een gastrostomie, wat gepaard gaat met intolerantie voor voeding en minor complicaties rondom het gastrostoma. Daarom zijn consultaties met een gespecialiseerde polikliniek en stomaverpleegkundigen belangrijk voor adequate begeleiding van patiënten en verzorgers. In de meerderheid van de patiënten wegen de voordelen van gastrostomie zwaarder dan de nadelige gevolgen.

REFERENTIES

1. Fortunato J CC. Outcomes of percutaneous endoscopic gastrostomy in children. *Curr Gastroenterol Rep* 2011;13(3):293–9.
2. Khattak IU, Kimber C, Kiely EM, et al. Percutaneous endoscopic gastrostomy in paediatric practice: Complications and outcome. *J Pediatr Surg*. 1998;33(1):67-72.
3. Srinivasan R, Irvine T, Dalzell M. Indications for percutaneous endoscopic gastrostomy and procedure-related outcome. *J Pediatr Gastroenterol Nutr*. 2009;49(5):584-588.
4. Gauderer MW, Ponsky JL, Izant RJ, Jr. Gastrostomy without laparotomy: A percutaneous endoscopic technique. *J Pediatr Surg*. 1980;15(6):872-875.
5. Georgeson KE. Laparoscopic gastrostomy and fundoplication. *Pediatr Ann*. 1993;22(11):675-677.
6. Collins JB,3rd, Georgeson KE, Vicente Y, et al. Comparison of open and laparoscopic gastrostomy and fundoplication in 120 patients. *J Pediatr Surg*. 1995;30(7):1065-70.
7. Akay B, Capizzani TR, Lee AM, et al. Gastrostomy tube placement in infants and children: Is there a preferred technique? *J Pediatr Surg*. 2010;45(6):1147-1152.
8. Zamakhshary M, Jamal M, Blair GK, et al. Laparoscopic vs percutaneous endoscopic gastrostomy tube insertion: A new pediatric gold standard? *J Pediatr Surg*. 2005;40(5):859-862.
9. Samson-Fang L, Butler C, O'Donnell M, AACPDM. Effects of gastrostomy feeding in children with cerebral palsy: An AACPDM evidence report. *Dev Med Child Neurol*. 2003;45(6):415-426.
10. Friedman JN, Ahmed S, Connolly B, et al. Complications associated with image-guided gastrostomy and gastrojejunostomy tubes in children. *Pediatrics*. 2004;114(2):458-461.
11. Noble LJ, Dalzell AM, El-Matary W. The relationship between percutaneous endoscopic gastrostomy and gastro-oesophageal reflux disease in children: A systematic review. *Surg Endosc*. 2012;26(9):2504-2512.
12. Rempel GR, Colwell SO, Nelson RP. Growth in children with cerebral palsy fed via gastrostomy. *Pediatrics*. 1988;82(6):857-862.
13. Corwin DS, Isaacs JS, Georgeson KE, et al. Weight and length increases in children after gastrostomy placement. *J Am Diet Assoc*. 1996;96(9):874-879.
14. Varni JW, Burwinkle TM, Seid M. The PedsQL 4.0 as a school population health measure: Feasibility, reliability, and validity. *Qual Life Res*. 2006;15(2):203-215.
15. Baker L, Beres AL, Baird R. A systematic review and meta-analysis of gastrostomy insertion techniques in children. *J Pediatr Surg*. 2015;50(5):718-725.
16. Petrosyan M, Khalafallah AM, Franklin AL, et al. Laparoscopic gastrostomy is superior to percutaneous endoscopic gastrostomy tube placement in children less than 5 years of age. *J Laparoendosc Adv Surg Tech A*. 2016;26(7):570-573.
17. Kang A, Zamora SA, Scott RB, et al. Catch-up growth in children treated with home enteral nutrition. *Pediatrics*. 1998;102(4 Pt 1):951-955.
18. Walker SP, Golden MH. Growth in length of children recovering from severe malnutrition. *Eur J Clin Nutr*. 1988;42(5):395-404.
19. Sullivan PB, Juszczak E, et al. Gastrostomy tube feeding in children with cerebral palsy: A prospective, longitudinal study. *Dev Med Child Neurol*. 2005;47(2):77-85.
20. Crosby J, Duerksen D. A retrospective survey of tube-related complications in patients receiving long-term home enteral nutrition. *Dig Dis Sci*. 2005;50(9):1712-1717.

21. Nguyen NQ, Fraser RJ, Bryant LK, et al. Functional association between proximal and distal gastric motility during fasting and duodenal nutrient stimulation in humans. *Neurogastroenterol Motil.* 2007;19(8):638-645.
22. Kawahara H, Dent J, Davidson G. Mechanisms responsible for gastroesophageal reflux in children. *Gastroenterology.* 1997;113(2):399-408.
23. Knatten CK, Avitsland TL, Medhus AW, et al. Gastric emptying in children with gastroesophageal reflux and in healthy children. *J Pediatr Surg.* 2013;48(9):1856-1861.
24. Kawahara H, Tazuke Y, Soh H, et al. Does laparoscopy-aided gastrostomy placement improve or worsen gastroesophageal reflux in patients with neurological impairment? *J Pediatr Surg.* 2014;49(12):1742-1745.
25. Sager S, Halac M, Selcuk N, et al. Temporal relationship between gastroesophageal reflux and rate of gastric emptying in children. *Nucl Med Commun.* 2010;31(12):1059-1062.
26. Kim S, Koh H, Lee JS. Gastroesophageal reflux in neurologically impaired children: What are the risk factors? *Gut Liver.* 2017 Mar; 11(2): 232–236.

Chapter 10

Review committee

List of publications

Dankwoord

Curriculum vitae

REVIEW COMMITTEE

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LIST OF PUBLICATIONS

Suksamanapun N, Mauritz FA, Franken J, Van der Zee DC, Lindeboom MYA. Laparoscopic versus percutaneous endoscopic gastrostomy placement in children: results of a systematic review and meta-analysis. *Journal of minimal access surgery* 2017;13(2):81-88.

Franken J, Mauritz FA, Suksamanapun N, Hulsker CCC, Van der Zee DC, Lindeboom MYA. Efficacy and adverse events of laparoscopic gastrostomy placement in children: results of a large cohort study. *Surg Endosc.* 2015 Jun;29(6):1545-52

Franken J, Mauritz FA, Stellato RK, Van der Zee DC, Lindeboom MYA. The effect of gastrostomy placement on gastric function in children: a prospective cohort study. *J Gastrointest Surg.* 2017 Jul;21(7):1105-1111.

Franken J, Stellato RK, Tytgat SHAJ, Van der Zee DC, Mauritz FA*, Lindeboom MYA* Gastrostomy placement in children does not increase gastroesophageal reflux: a prospective cohort study. *[Submitted]*

Franken J, Stellato RK, Tytgat SHAJ, Van der Zee DC, Mauritz FA*, Lindeboom MYA* Health-related quality of life in children after laparoscopic gastrostomy placement: a large cross-sectional study. *[Submitted]*

Franken J, Stellato RK, Tytgat SHAJ, Van der Zee DC, Mauritz FA*, Lindeboom MYA* The effect of gastrostomy placement on health-related quality of life in children: a prospective cohort study. *[Submitted for revisions at Journal of Pediatric Surgery]*

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CURRICULUM VITAE

Josephine Franken was born on the 6th of April 1991 in Amsterdam, the Netherlands. She is the middle one of three children of Theo Franken and Elsbeth Nijhuis. She spent most of her childhood in Deventer and attended high school at the Eddy Hillesum Lyceum, where she graduated cum laude at the gymnasium. After graduation she moved to Utrecht to study medicine at the University of Utrecht (2009).

During her study she enjoyed playing hockey (Utrecht Student Hockey Club) and joined the fraternity Collegium Studiosorum Veritas. In 2012 she went to Provincial Hospital Limbe in Cameroon for an extracurricular internship in Surgery. In 2013 she went to the Academic Hospital Paramaribo for her internship in Gynaecology. She worked as a student teacher at the clinical department. In the last year of medical school she completed her senior internships in general surgery at the University Medical Center Utrecht.

After graduating from medical school in december 2016 Josephine started working as a surgical resident (not in training), initially at the department of surgery in the Sint Antonius Ziekenhuis in Nieuwegein (supervisor dr. D. Boerma) for a period of 1,5 years, followed by the University Medical Center Utrecht (supervisor prof. dr. M.R. Vriens) for another year.

Early in her medical studies Josephine had a special interest in surgery. In her third year, she had started doing scientific research at the department of Pediatric Surgery in the Wilhelmina Children's Hospital supervised by prof. dr. D.C. Van der Zee, dr. M.Y.A. Lindeboom, dr. S.H.A.J. Tytgat and dr. F.A. Mauritz concerning laparoscopic gastrostomy placement in children. She presented results of her research at multiple international congresses of medical organizations, such as the European Pediatric Surgeon Association (2013) and the European Association for Endoscopic Surgery (2014, 2015). She completed this research along with her clinical activities and this eventually led to the completion of this thesis.

Josephine lives with Nick in Amsterdam.