Percutaneous endoscopic and radiologic gastrostomy

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Percutaneous Endoscopic and Radiologic Gastrostomy
Complications and outcomes for various indications and applications

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ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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- *What you think, you become.*
What you feel, you attract.
What you imagine, you create -

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A

GENERAL INTRODUCTION

Introduction and outline

1

General introduction

Direct access to the gastrointestinal (GI) tract via the stomach or small intestine is requested in several conditions and for various reasons, including nutritional support, decompression of the gastrointestinal tract, or the administration of medication (1).

First, nutrition accounts for the largest part of indications for enteral accesses (>90%)(2). In case oral feeding is impaired and in- or uptake of nutrients is deficient, malnutrition may occur. The risk of malnutrition is higher in a state of illness, due to increased caloric and nutrient demands. Moreover, a state of increased catabolism develops (3-5). Sufficient intake of nutrients is not always possible or simply too demanding during illness. Appetite may decrease, swallowing problems may occur, or the oro-esophageal-gastric route may be obstructed, stenotic, or dysfunctional in motility and transport. Malnutrition leads to decrease in fat free mass and body cell mass. As a result, malnutrition will negatively affect disease outcome, as well as physical and mental function (5-7).

Dietary advice, including high-caloric or nutrient and protein-rich supplements, more frequent meals, liquid meals in addition to regular meals, is first offered to improve nutritional status. When, despite these measures, a patient fails to meet the nutritional demands, supplementary or complete artificial nutrition (recently suggested to be replaced by the term 'medical nutrition therapy') might be necessary (3).

Enteral feeding is preferred for it is superior to parenteral feeding (total parenteral nutrition, TPN), because enteral administration of nutrients preserves gut function and has a lower complication rate than TPN (8-11).

Consensus has been reached that TPN is optional in case of inadequate enteral nutritional intake, or when enteral nutrition is considered unsafe, when the gastrointestinal tract is non-functional, inaccessible or leaking/perforated (9, 11).

To provide enteral access, several options are available. Short term enteral access is often achieved by a nasogastric tube (NGT), which has been practiced for more than 400 years. Other less frequently used options are the nasoduodenal tube (NDT), nasojejunal tube (NJT), oral gastric tube (OGT), and the oral duodenal tube (ODT). The major problem with these tubes is dislodgement, accompanied by an increased risk of aspiration. Furthermore, nasal or oral discomfort, ulceration, bleeding, clogging (because of a relatively small diameter), and poor cosmetics indicate that NGT (as well as NJT, OGT and ODT) are not suitable for longer use (8, 12-16).

The first description of a more sustainable enteral access was reported in 1635 by Schwaben, who described a gastrocutaneous fistula after removal of a foreign body from a man's stomach. In 1837, Egeberg suggested gastrostomy as a surgical procedure for the first time (17). Sédillot et al. reported the first surgical gastrostomy in 1849. All patients undergoing such procedures died, due to leakage of gastric contents from the fistula. From 1875, patients who survived with gastrostomies have been reported (17).

Cannulas and tubes were developed to minimize the loss of gastric contents (17-19). At first, cone shaped gastrostomies were used, but these were later on replaced by catheters. The first internal bolsters were introduced by Pénierés and Fontan, who described using a valve at the internal site (17). Gauderer and Ponsky developed a technique in which laparotomy was no longer necessary, with the assistance of gastrostomy. In 1980, they published the first report of a Percutaneous Endoscopic Gastrostomy (PEG) technique. Originally, the procedure was applied in high-risk children, however it seemed equally applicable in adults (20). PEG rapidly became popular in both pediatric and adult patients. Over time, it started to replace the surgical gastrostomy more and more because of its feasibility, lower morbidity, the fact that general anesthesia is not required, and the quick recovery after the procedure. In addition to these advantages, costs were lower because of shorter procedural time and faster hospital discharge (17, 21, 22).

PEG has evolved over the years into the current method of choice in medium- and long term enteral feeding (enteral feeding expected to last ≥ 30 days)(8, 12, 16) and has also been shown to be superior to NGT with respect to nutritional efficacy (23, 24) and patient preference (25-27). Nowadays, surgical placement is mostly performed laparoscopic, but only in cases where endoscopic PEG placement is not possible (1, 8, 12). Other options, such as radiologic placement, or placement of a percutaneous tube at other gastrointestinal locations (such as the jejunum and colon) will be discussed.

A PEG is nowadays considered a minimally invasive procedure and is commonly used in current practice. On the other hand, complications regularly occur and most patients in need for a gastrostomy are frail and undernourished. Hence, early recognition of the conditions requiring PEG placement and awareness of the potential complications of PEG placement will help to further improve the clinical efficacy of nutritional support via PEG.

Indications

As stated before, administration of nutrients is the most common reason to place a PEG catheter. Dysphagia is most frequently underlying this demand and may be caused by neurological disorders such as Cerebrovascular Accident (CVA) or Motor Neuron Disease (MND). Obstruction of the esophagus by a tumor or stenosis is another condition necessitating PEG placement (1, 8, 12, 15). Malnutrition due to impaired intake or impaired absorption of nutrients also is an indication. When the GI tract is functional and has sufficient length and absorptive capacity, enteral feeding should always be tried (1). PEGs are often placed prophylactically in patients with head and neck cancer as well, prior to the start of chemoradiotherapy, for this therapy may cause severe mucositis, limiting oral intake (28-30). Apart from nutritional demands, PEG can be used for other indications. These include the administration of medication, e.g. in Parkinson disease: continuous jejunal administration of Carbidopa-Levodopa(1, 31), or mechanical decompression of the stomach (32-35). Management of

gastric volvulus is a rare but useful indication for PEG, as well as drainage of gastric juices in case of a chronic gastrointestinal stenosis or ileus (8, 17).

An overview of indications for PEG is stated in Table 1.

Table 1. Indications for PEG (8, 36)

Indication	Examples
Neurogenic dysphagia	CVA Traumatic brain injury (cognitive impairment and depressed consciousness) Cerebral palsy Neurodegenerative syndromes such as MND*
Head and Neck Cancer (HNC)	Physical tumor obstruction In case side effects of treatment (e.g. mucositis) prevent adequate oral nutrition Local neurological involvement
Additional nutritional supplementation	Severe burns Hydrocephalus Severe congenital heart disease Anorexia Profound depression Dementia (although controversial)
Impaired absorption due to systemic illnesses	Crohn's disease Radiation enteritis Systemic sclerosis
Oral/throat surgery	Inability to eat, loss of swallowing function
Gastric decompression	Gastroparesis Malignant bowel obstruction
Drainage	Chronic gastrointestinal stenosis or ileus
Management of gastric volvulus	Fixation of stomach
Administration of medication	Parkinson disease

*MND = Motor Neuron Disease (including Amyotrophic Lateral Sclerosis (ALS), Multiple System Atrophy (MSA))

Contraindications

Contraindications for PEG include high-risk patients and conditions that prohibit placement. All absolute and relative contraindications are stated in Table 2. Some of these are not absolute, but relative and are currently under debate.

Table 2. Contraindications for PEG

Absolute	Active peritonitis
	Bowel ischemia
	Gastro-intestinal tract obstruction (unless the indication is decompression)
	Portal hypertension and gastric varices
	Severe erosive gastritis/ulcerations
	Tumor infiltration around puncture site
Relative	Uncorrected coagulopathy
	Ascites
	Large hiatus hernia and gastric volvulus
	Interposition of organs (colon, liver)
	Long-term (combined) immunosuppression, steroid use
	Open wounds
	Previous incisional hernia mesh repairs
	Adjacent stoma sites
	Peritoneal carcinomatosis
	Obesity
	Hemodynamic instability

Ascites

Safe placement in mild to moderate ascites has been described, mostly in patients with malignant ascites (37-39). In patients with decompensated cirrhosis, mortality rates after PEG do seem higher compared to compensated patients (in a case series of 26 cirrhotic patients undergoing PEG, 9/10 patients who died within 30 days had ascites)(40). However, evidence is limited. With pre-procedure paracentesis, no increased risk at infection or other complications was found both in malignant and cirrhotic ascites (37, 41). Cases in which PEG was placed safely in the presence of massive ascites have been described (42, 43). Nevertheless, ascites should be considered as a relative contraindication with careful risk-benefit assessment before the procedure.

Previous abdominal surgery

Previous abdominal surgery is not an absolute contraindication for PEG placement. Success rates are comparable to patients without previous surgery (44, 45). Even when PEG is placed two weeks post laparotomy in patients after various abdominal operations, complications are in the range of other patient groups. Other studies report on similar complication rates after giant hernia, abdominal compartment syndrome surgery, and Billroth partial gastrectomy when successful transillumination is accomplished and a negative needle aspiration test (puncture towards the stomach under continuous aspiration without prior air aspiration)(8, 45-48).

Ventriculoperitoneal drain

The presence of a ventriculoperitoneal (VP) drain/shunt is not accompanied by an increased rate of complications, if the VP shunt site is completely healed, the area of the shunt is avoided for PEG placement and antibiotic prophylaxis is given (to prevent both PEG site infection and VP shunt infection) (49-53). An increased risk of meningitis is feared but has not been shown in literature: no meningitis was reported using prophylactic antibiotics (12, 52, 53).

Pregnancy

Several case studies described safe and effective use of PEG in hyperemesis gravidarum during pregnancy, without major complications. Close monitoring of the fetus is advised, as well as ultrasound guidance. The pressure on both bumpers should be monitored closely, as enlargement of the uterus might lead to pressure enlargement and thereby necrosis. Conversion to a Percutaneous Endoscopic Jejunostomy (PEJ) might be considered in case vomiting persists with PEG (54-58).

Peritoneal Dialysis (PD)

Peritoneal dialysis is not a contra-indication to PEG. Good results have been reported with placement of PEG prior to the start of PD. Placement during PD might however be accompanied by an increased risk of peritonitis (59-61).

Obesity

Literature on obese patients receiving PEG is lacking. It should be acknowledged that malnutrition may occur in (morbid) obesity. In 1992, successful placement in a 170 kg patient was reported (62). A case series of six critically ill morbidly obese patients described conventional PEG placement without complications. The authors obtained transillumination by significant digital pressure on the area with least fat tissue density. However, even without full transillumination, placement was safe (44). This small study challenges the statement that obesity is a contra-indication for PEG.

Ethical considerations

Quality of life

Prior to gastrostomy insertion, several aspects should be acknowledged: indication for PEG placement, current condition and prognosis and patient's preference. Apart from that, ethical issues and the expected effect on quality of life and health status are important to consider (15, 63-66).

Certain algorithms have been presented to assist in the decision making. To offer PEG, the patient must be able to benefit from the nutrients given, must experience certain aspects of quality of life (doubted in case of a permanent vegetative state), and must have a life expectancy of >6-8 weeks

(otherwise NGT feeding can be sufficient). Otherwise, the physician can recommend against PEG, because of complications. The ethical issues in incapacitated patients with poor cognitive state, e.g. in advanced dementia, are very complex. Mostly, recommendations are against PEG placement. The decision should be based on what the patient wishes, and in case of mental incapability, what the caregivers consider best care (63-67). Thus, many aspects should be considered prior to placement of PEG in order to achieve a successful outcome.

Technique

Various techniques for PEG placement have been developed throughout the years.

The 'pull-method' is the most commonly used procedure to insert a PEG (first described by Gauderer and Ponsky (20, 68)). The 'push' method is a less frequently used method, described by Hashiba et al. in 1984 (69).

Preparation

Patients undergoing PEG placement must fast for at least six hours prior to the procedure.

Prevention of complications

Bleeding

PEG is considered a high-risk procedure with respect to bleeding. Therefore, recommendations for the management of patients using anticoagulants or antiplatelet therapy have been made.

Anticoagulants such as coumarins should be stopped prior to the procedure (acenocoumarol 3-4 days, fenprocoumon 5-7 days). In high risk patients, which include patients with prosthetic metal heart valve in mitral position, prosthetic heart valve and atrial fibrillation (AF), AF and mitral stenosis, and <3 months after venous thromboembolism, bridging with Low Molecular Weight Heparin (LMWH) is recommended.

P2Y12 receptor antagonists (clopidogrel, prasugrel, ticagrelor) should be stopped 5 days before the procedure, in case of coronary artery stents, consultation of a cardiologist is recommended.

Direct Oral Anticoagulants (DOACs) are recommended to be stopped at least 48 hours before the procedure, depending on renal function in case of dabigatran. However, no studies have been performed examining bleeding risk in PEG placement in patients with prasugrel, ticagrelor, or DOACs. Acetylsalicylic acid and/or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) can be continued.

Prothrombin Time (PT) is measured in advance, and indicated as the International Normalized Ratio (INR). Prior to placement, INR should be below 1.5 and otherwise be corrected. Other routine tests are not recommended (e.g. platelet count, hematocrit)(12, 15, 70).

Infection

Risk reduction can be accomplished by administering antibiotics prior to the procedure. The most recent systematic review (2013) showed a percentage of 9.4% when given intravenous antibiotics, compared to 24.2% when given placebo or no antibiotics (71).

The European Society for Clinical Nutrition and Metabolism (ESPEN) guideline states the use of antibiotic prophylaxis is not mandatory in experienced hands under established hygienic conditions, although it is recommended in cases of doubt or less experience (8). The American Society for Gastrointestinal Endoscopy (ASGE) and British Society of Gastroenterology (BSG) however highly recommend a single gift of parenteral cefazolin (2g)(15) resp. amoxicillin-clavulanic acid (72) 30-60 minutes before start of the procedure. Antibiotic prophylaxis is not necessary in patients already receiving appropriate broad-spectrum antibiotics around the time of the procedure, to lower the risk of Methicillin-Resistant *Staphylococcus aureus* (MRSA), which is commonly found in infected PEG sites (15, 72). Some studies found beneficial results in pre-screening for MRSA (73, 74).

Sedation

PEG is in general performed under conscious sedation, mostly with intravenous midazolam (+/- 5 mg), sometimes combined with fentanyl. Pulse oximetry is used for monitoring (75).

Placement

Pull method

After excluding upper gastrointestinal pathology during a routine gastroscopy, the stomach is inflated with air by a gastroscope so the stomach wall lies against the abdominal wall. Transillumination is used to find an appropriate puncture site, combined with pressing the skin while watching the impression on the inside. Besides that, during infiltration of the skin with local anesthetics, the needle must easily puncture through skin, abdominal wall and stomach wall without interference of other organs. In case no transillumination is obtained, a needle aspiration test is performed. When positive, advice is not to pursue with the PEG procedure but switch to a PRG placement under ultrasonographic guidance (76).

After making a small incision of maximum 1 cm at the puncture site, a trocar is placed. Through the trocar, a guidewire is inserted in the stomach and pulled endoscopically through the esophagus and mouth. The stomach part of the PEG is placed at the end of the guidewire (at the side of the mouth) and pulled towards the stomach by traction at the other side (abdominal skin). The PEG is pulled partially through the abdominal wall. At the inside of the stomach a 'bumper' is pulled against the stomach wall. The other side of the PEG is placed at the side of the skin and pulled (under light

traction) towards the abdominal wall. The external bolster is attached to the PEG and placement is finished (20).

Figure 1. PEG connection set (printed with permission of Freka®)

Push method

The push technique is a different method of PEG insertion (69). Instead of pulling the tube throughout the abdominal wall from the inside, it is pushed through from the outside. After insertion of the endoscope, four T-fasteners are placed at the marked PEG site. The stomach is thereby secured to the abdominal wall (to prevent displacement of the gastric wall). A guidewire is then pushed through the abdominal wall, visualized endoscopically. Dilators (trocar) are passed over this guidewire to create the stoma tract. The tube is then pushed over the guidewire and placement is finished. The T-fasteners are removed after 12 days.

Advantages of this technique include use of a smaller endoscope (e.g. in case of stenosis), or even transnasal endoscopy with an ultra-thin caliber endoscope (UTCE)(77, 78). With UTCE, sedation is not necessary, which makes it feasible for patients with severe (pulmonary) comorbidities.

Avoidance of oropharyngeal contamination of the tube is another advantage of the push technique. Similar rates of infection with the push method without antibiotic prophylaxis were observed compared to the pull method with antibiotic prophylaxis (79, 80). However, also similar infection rates without use of antibiotic prophylaxis in both techniques have been reported (81). Despite lower

risk of infection, a significantly higher complication rate was reported with push PEGs compared to pull PEGs with significantly higher dislocation and occlusion rates (0-3.8% in pull PEGs vs. 10-12% in push PEGs) (79, 81).

Success rates in PEG range from 84-100% (82-85). No differences in success rates between the push and pull method have been reported, however the conventional pull method is considered easier to perform (86, 87).

Figure 2. Push-PEG tube with filled balloon (printed with permission of Freka®)

Initiation of feeding

Feeding can be started immediately or within 1-2 hours after placement (1, 12). Previously, starting of feeding was recommended 12-24 hours after placement, however several randomized studies demonstrated that early initiation of feeding is safe (88-90).

Aftercare

The first three days, the insertion site should be cleaned daily with water, without moving the tube. After a week, in which the fistula forms, the tube needs daily movement (carefully pushing it 2-3 cm ventrally and pulled back up to resistance) and a daily 360° turn, to avoid adhesions and buried bumper syndrome (described in 'General discussion')(11, 12).

After maturation of the stoma canal, the PEG system may be changed for a button-system, mostly for cosmetic reasons. More recently, safe direct button placement using the push technique has been described (91). The higher price and necessity for routine change (every six months) make these systems only indicated in young patients, in order to reach a more cosmetically acceptable look (92).

Complications of PEG

Although PEG placement is safe and well tolerated in the majority of patients, complications may occur; reported rates vary considerably (overall reported rates between 4.9% and 40% (8, 15, 93)), depending on patient selection and different manners of scaling. The majority consist of minor complications, with major complications in 0.4% to 5% (15).

Close follow-up is indicated, including assessment of the surrounding skin, location of the tube, approximation of the tube to the abdominal wall, and avoiding excessive traction on the PEG.

Periprocedural complications

Periprocedural complications are mostly respiratory, such as laryngospasm, aspiration, respiratory depression or apnea, desaturation or airway obstruction (94). Aspiration related to the procedure is reported in approximately 0.3-1.0% of cases (95-97).

Post procedural complications

Post procedural complications are divided into early (≤ 30 days) or late (> 30 days) and classified as minor or major (12). Complications include site infection, bleeding, peristomal leak, pneumoperitoneum, peritonitis, buried bumper syndrome, aspiration pneumonia, dislocation, obstruction and tumor seeding (1, 2, 12, 15, 95, 98-110). Mortality related to PEG placement is mostly due to aspiration pneumonia or peritonitis and occurs in 0-2% of cases (111-117). An extended description of complications, mortality and known risk factors is stated later on in this thesis.

Other applications

Percutaneous Endoscopic Gastrostomy with Duodenal/Jejunal extension (PEG-J) or Percutaneous Endoscopic Jejunostomy (PEJ)

Duodenal/jejunal feeding by PEG has been described since 1984 by Ponsky, first with extension of a PEG, and use of PEJ in patients with previous gastrectomy (118, 119). Duodenal or jejunal feeding is indicated in patients unable to receive a gastric tube due to altered anatomy (e.g. after gastrectomy), patients who cannot tolerate gastric feeding (e.g. gastroparesis or generalized motility disorders), patients with severe Gastro-Esophageal Reflux Disease (GERD), and in case intraduodenal administration of medication is required (e.g. continuous duodopa in Parkinson's disease).

Duodenal/jejunal feeding has long been believed to encounter a lower risk for aspiration than gastric feeding and thereby offered to patients with a high risk of aspiration (120, 121). Literature shows conflicting data on this behalf, debating this statement (122-124).

Percutaneous Endoscopic Gastrostomy with duodenal/jejunal extension (PEG-J)

In PEG-J, PEG is inserted by the pull method, immediately followed by a duodenum/jejunum extension tube, lead through the PEG tube. The extension is pulled to the distal duodenum or proximal jejunum (at or near the ligamentum of Treitz) endoscopically with a grasping forceps, and fixed with an hemoclip. Common complications are dislocation (27-36%)(125-127) and occlusion (3.5-35%) of the duodenal-jejunal extension, which is smaller than the regular PEG tube. Other complications are comparable to PEG (127-129).

Percutaneous Endoscopic Jejunostomy (PEJ)

PEJ (also referred to as Direct PEJ (DPEJ)) is a technique to directly place a jejunostomy. The technique is similar to pull-PEG, with the only difference that the infiltration needle is fixated into the small bowel lumen with a snare or grasping forceps, to prevent migration of the punctured bowel. The trocar is inserted next to and in the same direction as the infiltration needle, using this as a guide to the bowel lumen. The tube is placed directly in the jejunum.

Disadvantages of this procedure are a relatively low success rate (68-90%), due to technical difficulties; advancement of a needle directly into the narrow jejunum lumen is difficult (130-132). However, with the introduction of Double Balloon assisted PEJ, success rate of 90-96% are reported (133-135). The largest series to date reported a high percentage of complications of 10% (136), which is certainly higher than in PEG-J. Moreover, if gastric decompression is needed, a separate gastrostomy tube is required, whereas with PEG-J this can be combined. An advantage of PEJ is better reliability than PEG-J, with an approximately four times lower replacement rate (125, 132, 136).

Percutaneous Transesophageal Gastro-tubing (PTEG)

PTEG was developed by Oishi et al, who described gastrostomy tube placement in the esophagus in their first report in 2003 (137). This technique can be used in case a PEG is impossible or contra-indicated (e.g. patients with a total gastrectomy or massive ascites).

First, a rupture-free balloon is inserted in the esophagus through the nose and inflated. Under ultrasonographic vision, the balloon is punctured through the left neck, just below the thoracic outlet. After insertion of a guidewire through the needle, the punctured site is dilated (using a dilator with sheath). Afterwards, the tube is inserted and the sheath is removed.

It turned out to be as safe as PEG in several small studies (137-141), however evidence is still limited and the technique is currently not commonly used. This procedure is not well known among gastroenterologists and radiologists, but in cases when gastrectomy has been performed this option should be considered, as publications on this technique report that it is a safe procedure.

Percutaneous Endoscopic Colostomy (PEC)

In 1986, the application of a PEG tube in the cecum (Percutaneous Endoscopic Cecostomy) was described as an alternative treatment method for nonobstructive dilatation of the colon (142) and pseudo-obstruction (143). In 1999, Daniels et al. described the first Percutaneous Endoscopic Colostomy for incontinence and constipation (144). The technique is similar to the pull method in PEG, with placement in the colon.

PEC is used for antegrade lavage in patients with refractory constipation, without the need of oral intake of large volumes of laxatives. Other applications are decompression/desufflation of the colon, or fixation of the sigmoid in case of recurrent volvulus and in case of severe fecal incontinence (e.g. in patients with neurologic diseases such as cerebral palsy or spinal cord injuries)(145-147).

Alternative options to PEG

Percutaneous Radiologic Gastrostomy (PRG)

Shortly after development of PEG, a radiologic option became available. Percutaneous Radiologic Gastrostomy (PRG) was first described in 1981 by Preshaw (148). It is a Seldinger technique in which the stomach is insufflated with air following the passage of a small nasogastric tube or per oral catheter. A needle is pushed percutaneously into the stomach under fluoroscopic or ultrasound guidance and a wire passed through the needle. A gastrostomy tube is then passed over the wire. In case finding a safe window by fluoroscopy is difficult, Computed Tomography (CT) guidance can be used (149). The high radiation exposure withholds from using CT in every patient. Indications for PRG are comparable to PEG.

Contraindications

Contraindications for PRG placement include altered gastric anatomy or location (e.g. displacement by an intra-abdominal tumor). Massive ascites is a contraindication as well, with a 7.7 times higher risk at infectious complications (36, 150), although O'Keeffe et al. reported successful placement in patients with mild to moderate ascites (151).

PRG avoids the risk of oropharyngeal contamination as occurs in PEG. Hence, the risk of infection is believed to be lower than with PEG and routine antibiotic prophylaxis is not recommended (12). Moreover, in case of stenotic tracts or obstructing tumors, PRG can be feasible (107, 108, 152).

Disadvantages of PRG include radiation exposure, dislocation due to less solid fixation, and occlusion because of smaller tube sizes. Besides that, routine changes are necessary every 3-6 months (36, 113).

Figure 3. PRG tube. Printed with permission from Cook Medical®

Per-oral Image Guided Gastrostomy (PIG)

PIG is a hybrid technique, developed in 1988, using fluoroscopic guidance to puncture the stomach (153). After this puncture, a guidewire is introduced to catheterize the esophagus in a retrograde manner. A gastrostomy tube is then pulled through the mouth to the abdominal wall.

The advantages of this technique are the fact that solid, large diameter tubes can be placed without or minimal use of sedation. Besides that, it can be performed with concomitant use of Non Invasive Positive Pressure Ventilation (NIPPV)(83, 153, 154). It is a safe alternative with a high technical success rate (98-99%) and similar complication rates compared to PEG and PRG (155-158).

It seems a decent option if endoscopic placement is not possible but a more solid or larger tube is preferred than possible with PRG. It is however not widely used at the current time, probably due to lack of expertise (36).

Surgical gastrostomy

Several surgical techniques for gastrostomy were available before PEG was developed. Open gastrostomy placement can be performed according to the Witzel, Stamm or Janeway procedures. The Witzel technique uses an anterior seromuscular sleeve surrounding the catheter. Stamm gastrostomy is based on creating an invagination (lined with serosa) with concentric pursestring sutures and was described in 1984. The Janeway fistula is made by a gastric wall flap, and has been used more frequently after the development of stapling devices to create the fistula out from the stomach (17).

Due to lower complication rates, surgical tubes are currently placed laparoscopically (Percutaneous Laparoscopic Gastrostomy, PLG). A gastrostomy tube is placed under direct laparoscopic vision, after sutures are placed to perform gastropexy, first through the anterior gastric wall, then externalized through an incision at the skin site. PLG is a more complicated procedure than PEG, requires general anesthesia, and is accompanied by higher costs, for operating room facilities are needed. The possibility to visualize the anatomy and placement of a surgical gastropexy are in favor of PLG (159-161). PLG seems at least as safe as PEG and might therefore be the method of choice when PEG or PRG is not possible (162, 163).

Surgical laparoscopic jejunostomy

Laparoscopic jejunostomy can be indicated in case of difficult laparoscopic gastrostomy or in case endoscopic jejunostomy is not possible. General anesthesia is required, and the procedure is more expensive than percutaneous placement (164, 165).

Two methods are used, the first being the same as in surgical gastrostomy, but with placement of the tube in the jejunum. Secondly, a technique using T-fasteners has been described as an alternative. Four trocars are placed, with one being the landmark for tube placement. Four sutures are placed on a selected loop of the jejunum (in a diamond shape), on the antimesenteric side. A suture grasper is used to extract these stitches, through incisions around the landmark trocar. A 12Fr catheter is inserted into the bowel after removing the trocar. The sutures are pulled towards the abdominal wall and tied to the wall (166, 167).

Conclusion

PEG is the first choice technique for enteral feeding expected to last ≥ 30 days. Indications for PEG are numerous, including dysphagia (e.g. neurogenic after CVA or in MND) and malnutrition (e.g. impaired intake or absorption of nutrients).

Although it is considered minimally invasive, complications occur regularly. Periprocedural complications include laryngospasm, aspiration, and sometimes respiratory depression. Post procedural complications such as site infection, bleeding, peritonitis, buried bumper, are classified as minor and major, and may occur early (≤ 30 days) or late (>30 days after the procedure). Mortality after PEG is rare. Complications have been described, not only procedure related but also disease related. Alternative applications of PEG include PEG-J, PEJ, and PEC. Use of these alternatives is not common and use in certain patients or conditions such as gastroparesis or refractory constipation has not (often) been described.

Available alternatives for PEG placement are PRG, PIG, and surgical gastrostomy. No consensus is reached yet about which technique is best considering outcomes and complications for different patient groups.

Aim and outline of the thesis

In this thesis, we have aimed to systematically evaluate indications, efficacy and complications of Percutaneous Endoscopic Gastrostomy, as well as show other applications (e.g. PEC, PEG-J), and to compare it to its radiologic alternative PRG.

The first part of this thesis (**Chapter 2&3**) focuses on the comparison of PEG with PRG, in order to determine the advantages of both techniques in different patient categories.

Chapter 2 is an extended systematic review and meta-analysis comparing PEG and PRG. Tube related complications, infectious complications, procedure related mortality and 30-day mortality, for all indications, were analyzed. Subgroup analysis for patients with head and neck cancer as well as motor neuron disease were performed.

Chapter 3 focuses on complications in PRG and PEG in the largest series to date, with a total of 760 patients. This retrospective single center cohort study aimed to analyze mortality and complications, in order to be able to predict which patients are most eligible for PEG, and which for PRG.

The second part of this thesis (**Chapter 4&5**) addresses complications in PEG. First, a new method in preventing infectious complications in PEG is described (**Chapter 4**), using antibiotic gauzes around the insertion site, instead of prophylactic systemic antibiotics.

Chapter 5 investigates the placement of PEG in a very vulnerable group; patients with Amyotrophic Lateral Sclerosis. Our study is the first to describe placement of PEG under conscious sedation, without using Non Invasive Ventilation during the procedure.

Alternative applications of PEG are described in the final part of this thesis (part 3). The use of PEG-J and other treatment modalities in gastroparesis is studied in **Chapter 6**.

We aimed to determine the effect of different nutritional treatment modalities (diet and prokinetics, gastric rest with nasoduodenal feeding, and enteral feeding by PEG-J) on subjective and objective parameters. We hereby describe for the first time the results of a group of tertiary referred gastroparesis patients treated by PEG-J.

Chapter 7 describes the use of PEC in patients with refractory constipation, including a long-term follow-up.

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Finally, **Chapter 8** summarizes the main finding of all studies in this thesis, as well as discussing new insights, future perspectives, implications for future research, and future applications.

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B

PEG VERSUS PRG

A Systematic Review and Meta-analysis on outcomes and complications of Percutaneous Endoscopic versus Radiologic Gastrostomy for enteral feeding

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2

Abstract

Background

The optimal technique for long term enteral feeding has not yet been established. Both Percutaneous Endoscopic Gastrostomy (PEG) and Percutaneous Radiologic Gastrostomy (PRG) are widely used. Aim was to extensively review outcomes of PEG and PRG.

Patients and methods

A systematic review using Medline, Embase, and Cochrane was performed, using standardized tools for assessing bias. Main outcomes were infectious and tube related complications, procedure related and 30-day mortality. Pooled risk differences (RD) with corresponding 95% confidence intervals [95% CIs] were calculated using random effects. Arcsine transformations were applied.

Results

344 studies were identified, of which 16 were included, reporting on 934 PEGs and 1093 PRGs. No differences were found for infectious complications (RD 0.03 [-0.05 - 0.11]), procedure related mortality (RD 0.01 [-0.04 - 0.06]), or 30-day mortality (RD 0.06 [-0.01 - 0.13]). Tube related complications were higher in PRG (RD 0.16 [0.06 - 0.26]). Subgroup analysis was performed for head and neck cancer (HNC) and Motor Neuron Disease (MND). In HNC, this revealed significantly lower tube related complications and procedure related mortality after PEG. In MND, no differences were seen. The level of evidence appears sufficient considering the low degree of heterogeneity.

Conclusion

No differences were found with regards to mortality or infectious complications. PEG showed lower risk of tube related complications. Subgroup analysis revealed PEG to be favorable in HNC based on lower rates of procedure related mortality and tube related complications. Local experience and availability should be taken into account in the decision process.

Introduction

Gastrostomy feeding is preferred over nasogastric tube feeding when medium and long-term enteral feeding (≥ 4 weeks) is indicated (1). In case the gastrointestinal tract is available for digestion and absorption of nutrients, enteral nutrition has proven to be superior to parenteral nutrition: it improves nutritional outcome, reduces associated morbidity, and preserves gut function (2). The optimal technique for long-term enteral feeding has not yet been well established. Both Percutaneous Endoscopic Gastrostomy (PEG) and Percutaneous Radiologic Gastrostomy (PRG) are widely used techniques. Most common indications for gastrostomy placement include head and neck cancer (HNC, often prophylactic before start of chemoradiotherapy), Motor Neuron Disease (MND), other neurologic disorders, e.g. a cerebrovascular accident (CVA), and malnutrition (e.g. post-surgical recovery, mental retardation, motility disorders of the gastrointestinal tract).

Complications and mortality of both techniques have previously been reported, but separately. Consensus on which technique is more favorable has not been reached up to now. Most patients in need for a gastrostomy are vulnerable and malnourished. Therefore, when choosing between PRG and PEG, it is of utmost relevance to take into account procedure related complication and mortality risks. It appears that 30-day mortality is relatively high both in patients undergoing PEG or PRG procedures (3-5). This has been associated with poor patient selection. Several risk factors for 30-day mortality have previously been identified. These include higher age, lower body mass index (BMI)(6), C-reactive protein (CRP) $> 21.5\text{g/L}$ (7, 8), Diabetes Mellitus (8), albumin $< 3\text{g/d}$ (7, 9), radiotherapy, cirrhosis, cancer (10), Chronic Obstructive Pulmonary Disease (COPD), and residing in a nursing home (7).

Previous publications have indicated that infectious complications occur at rates of 8-15% (1, 11) in PEG and 2-22% in PRG (3, 12, 13). In PEG, antibiotic prophylaxis significantly reduces the risk of infectious complications, as shown in a meta-analysis by Lipp et al., leading to a decrease from, 24.2 to 8.4% (11). The benefit of antibiotic prophylaxis in PRG is less clear (12, 14). Generally, antibiotics are not administered because the risk of peristomal infection is considered to be lower in PRG due to a lower risk of contamination as the tube does not pass the oropharynx. Tube related complications such as dislocation, obstruction, leak, or rupture are reported in 1.7-15% in PEG and 5.2-57% in PRG (3, 4, 15).

In the past, a few systematic reviews including meta-analyses were performed comparing PEG to PRG (12, 16, 17). However, these meta-analyses have certain limitations as they generally focused only on a single outcome or included studies of low quality. Conclusions of these meta-analyses should therefore be interpreted with caution. A confirmative meta-analysis based on representative data is therefore warranted.

Chapter 2

Our aim was to perform a systematic review of the literature and meta-analyses for outcomes of PEG and PRG in order to delineate the best suitable options for specific groups of patients and also for individual patients. Based on previous literature, we expected to encounter higher tube related complications for PRG, slightly higher infectious complications in PEG, and a comparable 30-day and procedure related mortality for PEG and PRG.

Methods

Methods and inclusion criteria were specified prior to the study and have been documented in a protocol. The search was performed by the main and second investigator in collaboration with an experienced librarian.

Studies were identified by searching electronic databases according to the PRISMA guidelines, including hand searching of reference lists of articles and consultation with experts in the field if necessary. Search terms used were complication(s), adverse event(s) or effect(s), PEG, PRG, and their synonyms. No publication date, or publication status restrictions were imposed. No limits were applied for language and foreign papers were translated. The search was applied to Medline (1966 – 2-5-2017) and adapted for Embase (1980 – 2-5-2017). Cochrane and DARE (Database of Abstracts of Reviews of Effectiveness) databases were reviewed.

Study Selection

Types of studies included were randomized clinical trials and retrospective reviews/cohort/case-control studies. A selection list by title and abstract was made. Eligibility assessment was performed independently in an unblinded standardized manner by 2 authors (DS and DK) according to PRISMA guidelines. Discrepancies between reviewers were resolved by consensus. A third reviewer was consulted in case disagreements remained (AM). Selection of outcomes was based on the clinical principles underlying the hypothesis. Reviews, case reports, surveys and irrelevant articles were excluded. 1 article was excluded from the synthesis for it did not meet the specific outcomes (28), and one article (29) resembled another, after contacting the authors, the results included were the same as in ProGas (3). Three studies were excluded because of a critical bias risk in one or more domains (30-32). Three studies were excluded for children were included in the same analysis as adults (16, 33, 34). We were unable to ascertain which outcomes specifically referred to adult or pediatric patients. Unfortunately, no clarifying information concerning this issue was received after contacting the authors.

Main outcome parameters were infectious and tube related complications (≤ 30 days), procedure related mortality and 30-day mortality. Amongst infectious complications we included peristomal infection and peritonitis. Absolute peritonitis rates were assessed as well. Amongst tube related complications we included dislocation, leak, obstruction, need for replacement, and defects (e.g. rupture, break down). Secondary outcome was the occurrence of tumor seeding. Characteristics of trial participants, type of intervention, and the trial's in- and exclusion criteria were extracted and classified in a data extraction sheet partially based on the Cochrane Consumers and Communication Review Group's data extraction template (19).

Chapter 2

We chose an extended review including observational studies as well, because of the lack/paucity of Randomized Controlled Trials (RCTs) on this subject. Conference abstracts were included as well. Case reports, literature reviews and letters to the editor were excluded. Studies describing a pediatric population (aged under 18) were excluded because we expected them to be not comparable to adults because of different physiology and different indications for gastrostomy, and thereby probably different complication rates.

Assessment of confounding

To ascertain the validity of eligible studies, standardized assessment tools (The Risk of Bias in Non-randomized Studies (ROBINS-I) (20) and Newcastle Ottawa Scale (NOS) (21)) were applied prior to inclusion. This was done for all four outcome levels separately and all together. Separate analysis did not change the overall result and therefore we only reported the overall result. The risk of bias due to confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result was determined. We have once had contact with authors in order to receive a full text copy of an article (18), however, no answer was obtained.

Statistical methods

Because of expected low complications risks, pooled risk differences with corresponding 95% confidence intervals were calculated. Random effects models with DerSimonian-Laird estimator to cover both within and between study heterogeneity were used. To correct for low complication rates an Arcsine transformation was applied, to stabilize variance in order to make the pooled outcome more reliable (22). The results were translated to the original scale and presented in Forest plots. Heterogeneity among studies was measured with the inconsistency index (I^2), where a value of minimal 50% was considered as substantial heterogeneity between studies (23). Possible publication bias was studied using Funnel plots with Egger's test for asymmetry (24). Two-sided p-values of 0.05 or lower were considered significant. We used the Metafor package version 1.9 (25) in R statistical program version 3.2.2 (26) to process all the collected data. The effect of single studies with different methodology was tested by sensitivity analyses in which pooled rates with and without this study were compared (26, 27). Subgroup analysis was planned for studies including only MND or HNC patients, and studies including a various population.

Results

455 citations were found (Figure 1, PRISMA diagram), with 344 unique citations. Criteria for eligibility were assessed by screening on title. No relevant articles in other languages than English or unpublished ongoing studies were found. Most articles were no head-to-head comparison, case reports, reviews, or not relevant. 68 articles were found eligible. Inclusion for qualitative assessment was based on abstract, reasons for exclusion are stated in the PRISMA diagram (Figure 1). A total of 16 studies were included in the quantitative meta-analysis (4 prospective non randomized, 12 retrospective studies), reporting on 934 PEGs (placed using the pull method (1)) and 1093 PRGs (3-5, 13, 15, 35-46). Study characteristics and the risk of bias are stated in resp. Table 1 and 2, including risk per domain (as stated in the ROBINS-I scale).

Overall results

In the overall population, no differences were found between PEG and PRG for procedure related mortality (RD 0.01 [95% CI -0.04 – 0.06], Figure 2), or 30-day mortality (RD 0.06 [-0.01 – 0.13], Figure 3), nor infectious complications (RD 0.03 [-0.05 – 0.11], Figure 4). Tube related complications (including dislocation, obstruction, leak and tube defects) were significantly lower in PEG (RD 0.16 [0.06 – 0.26], Figure 5).

Funnel plots are shown in Figures 6-9, absolute complication rates are stated in Table 3. Absolute peritonitis rates are stated in Table 4.

Figure 1. PRISMA diagram

Table 1. Study Characteristics

Author	Year	Country	Indication	Design	Period	PRG (n=)	PEG (n=)	Inclusion criteria	S/M*
Silas	2005	USA	All	Retrospective	1.1.1997-1.1.2001	193	177	All initial PEG/PRG	S
Laasch	2003	UK	All	Prospective, non randomized	1.7.2000-1.2.2002	50	25	All initial PEG/PRG	M (3)
Grant	2009	UK	HN	Prospective, non randomized	1.1.2004-1.1.2005	50	121	All initial PEG/PRG	M (4)
Möller	2009	Sweden	All	Retrospective	1.1.1990-1.12.1994	94	12	All initial PEG/PRG	S
La Nauze	2012	Australia	All	Retrospective	1.1.2007-1.4.2009	97	80	All initial PEG/PRG	S
Allen	2013	USA	MND	Retrospective	1.1.2009-1.3.2012	51	57	All initial PEG/PRG	S
Laskaratos	2013	UK	All	Retrospective	1.1.2009-1.7.2011	40	53	All initial PEG/PRG	S
Rustom	2005	UK	HN	Retrospective	1.2.2002-1.2.2005	28	40	All initial PEG/PRG	S
Galaski	2009	Canada	All	Retrospective	1.12.2004-31.12.2005	30	44	All initial PEG/PRG	S
Blondet	2010	France	MND	Retrospective	1.1.1999-1.1.2005	22	21	All initial PEG/PRG	S
Chio	2004	Italy	MND	Retrospective	PEG: < 2000 PRG >2000	25	25	FVC <50%, dysphagia weight loss>10%	S
Mc Allister	2013	UK	HN	Retrospective	1.1.2010-1.3.2013	89	21	All initial PEG/PRG	S
Desport	2005	France	MND	Retrospective	1.3.1996-1.11.2002	20	30	All initial PEG/PRG	S
ProGas	2015	UK	MND	Prospective	2.11.2010-31.1.2014	124	163	All initial PEG/PRG	M (24)
Rio	2010	UK	MND	Retrospective	1.1.1999-1.1.2006	121	21	All initial PEG/PRG	S
Elliot	1996	UK	All	Prospective, non randomized	1.1.1991-1.6.1994	45	33	All initial PEG/PRG	S

*S=Single center, M=Multicenter

Table 2. Risk of Bias

Author	ROBINS-I	ROBINS-I subscales					NOS		
	Overall	Bias due to Confounding	Bias due to selection into study	Classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall scale
Silas	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate	9/9
Laasch	Serious	Serious	Low	Low	Low	Low	Low	Moderate	7/9
Grant	Serious	Serious	Low	Low	Low	Serious	Low	Moderate	6/9
Möller	Serious	Serious	Low	Low	Low	Low	Moderate	Moderate	7/9
La Nauze	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate	7/9
Allen	Moderate	Serious	Low	Low	Low	Low	Low	Moderate	6/9
Laskaratos	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate	9/9
Rustom	Serious	Serious	Low	Low	Low	Serious	Low	Moderate	6/9
Galaski	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate	7/9
Blondet	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate	9/9
Chio	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate	8/9
Mc Allister	Serious	Serious	Low	Low	Low	Low	Low	Moderate	7/9
Desport	Serious	Serious	Low	Low	Low	Low	Low	Moderate	7/9
ProGas	Low	Low	Low	Low	Low	Low	Low	Low	8/9
Rio	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate	6/9
Elliot	Serious	Serious	Low	Low	Moderate	Low	Low	Moderate	7/9

Subgroup analysis

Subgroup analysis was performed in patients with HNC (349 patients) as well as MND (529 patients). Results are shown in combined Forest plots (Figure 2-5). In HNC patients, this revealed a significantly lower incidence in patients with PEG vs. PRG with respect to tube related complications (RD 0.15 [0.04 - 0.27]), as well as procedure related mortality (RD 0.14 [0.005 - 0.27]) (borderline significant). In MND, no differences were seen.

Table 3. Absolute rates of complications

	PEG	PRG
Procedure related mortality (Overall)	1%	1%
Various population	1%	1%
HNC	1%	5%
MND	1%	1%
30 day mortality (Overall)	7%	11%
Various population	10%	17%
HNC	1%	7%
MND	6%	7%
Infectious complications (Overall)	6%	7%
Various population	9%	7%
HNC	2%	5%
MND	8%	13%
Tube related complications (Overall)	6%	16%
Various population	8%	19%
HNC	4%	13%
MND	4%	4%

HNC= Head and Neck Cancer; MND=Motor Neuron Disease

Table 4. Absolute peritonitis rates

Peritonitis (Overall)	2.4%	0.7%
Various population	2.1%	1.4%
HNC	5.6%	0%
MND	0.01%	0%

Sensitivity testing

Sensitivity testing for infectious complications in HNC was performed, thereby excluding the study by McAllister et al. because the authors expected underreporting by patients, nurses and medical staff (47). Risk difference for HNC increased from a non-significant 0.11 [-0.06 – 0.28] to significant 0.19 [0.05 – 0.32] in favor of PEG. In the overall study population, RD increased from -0.03 [-0.05 – 0.11] to 0.04 [-0.04 – 0.12], both non-significant.

Three studies applied antibiotic prophylaxis in both PEG and PRG. No antibiotics were administered neither prior to PEG or PRG placement in nine studies, and in one study antibiotics were administered randomly. A difference in prophylactic antibiotic use between PEG and PRG was found in three studies (4, 40, 48). Antibiotics were only administered in PEG placement in these studies. One did not properly report infectious complications (40). The other two were excluded in sensitivity analysis because of the expected influence on the infectious complication rate. The RD in the overall study population remained non-significant in the overall pooled study population as well as in the subgroup.

Tumor seeding

No tumor seeding has been reported in the included studies, neither for PEG nor for PRG patients.

Heterogeneity

There was no evidence for heterogeneity amongst studies for most outcomes, with I^2 values of respectively 0% for procedure related mortality, 12% for 30-day mortality, and 39.12% for infectious complications. In tube related complications, heterogeneity was considerable ($I^2=59.83\%$). For all outcomes, Funnel plots were symmetric as confirmed by non-significant Egger's tests.

Figure 2. Forest plot of procedure related mortality

Figure 3. Forest plot of 30-day mortality

Figure 4. Forest plot of infectious complications

Figure 5. Forest plot of tube related complications

Figure 6. Funnel plot of procedure related mortality

Figure 7. Funnel plot of 30-day mortality

Figure 8. Funnel plot of infectious complications

Figure 9. Funnel plot of tube related complications

Discussion

We have performed a comprehensive meta-analysis that compared PEG to PRG on multiple outcomes and indications including 2027 patients. Overall, no differences were found between PEG and PRG with regard to mortality or infectious complications. Patients with PEG had a lower risk of tube related complications compared to patients with PRG.

Mortality

Pooled procedure related mortality rates were 1% both in patients receiving PEG and PRG (RD 0.01 [-0.04 – 0.06]). In a previous meta-analysis of 5680 patients, Wollman et al. reported a procedure related mortality of 0.53% for PEG and 3% for PRG (16), whereas Yeung et al. reported 0.3-1% for PEG and 0-1.9% for PRG (49). Our results are in the same range and confirm those of previously published meta-analyses.

An absolute 30-day mortality rate of 7% in PEG vs. 11% in PRG was found (RD 0.06 [-0.01 – 0.13]). The mortality rates found here are in line with a recent meta-analysis on 30-day mortality by Lim et al. including 2183 patients (17). However, Lim et al. found a statistically significant difference with regard to 30-day mortality (5.5% in PEG vs. 10.5% in PRG, (OR, 0.60; 95% CI, 0.44 – 0.82; P=0.001). Wollman et al. reported higher 30-day mortality rates for both groups: 14.7% in PEG vs. 15.4% in PRG (16), with no significant differences between PEG and PRG.

There are several methodological items that should be taken into account when comparing data from previous studies to our current analysis. First, we excluded studies that analyzed a single modality (PEG or PRG alone) instead of a direct comparison between both techniques. This selection criterion has not been applied in the previously published meta-analysis. Second, an important confounder is the general condition of the patient prior to gastrostomy, since this is a major factor influencing survival. Third, in order to minimize the influences from such effects, we have only included studies correcting for baseline differences in patients receiving PEG vs PRG. Fourth, we performed strict selection after quality and risk of bias assessment. For instance, Lim et al. included studies of low quality that were characterized by critical risk of bias (17). The earlier meta-analyses by Grant et al. and Wollman et al. entailed the same quality and selection bias issues (12, 16).

Tube related complications

Tube related complications occurred at rates of 6% in PEG vs. 16% in PRG (RD 0.16 [0.06 – 0.26]). This difference may be caused by several factors. First, the inflatable balloon retention mechanism and locking pigtail as used in PRG is less solid than the flange used in PEG, and thereby more prone to dislocation. Secondly, the smaller tube size in PRG (10-14Fr., mostly 12 Fr.) compared to PEG (15-24Fr., mostly 20Fr.) in all of the included studies, increases the risk of obstruction. Tube related problems result in additional hospital visits with discomfort for patients. This aspect was not

specifically addressed in the current analysis. In our opinion, these complications should be taken into consideration when deciding which type of gastrostomy is most suitable for a specific patient. In the meta-analysis by Wollman et al., tube related complication rate was significantly higher in PEG (16%) than in PRG (12.1%), contrary to our results (16). It should be acknowledged that these studies were at high risk of bias without a head-to-head comparison, as previously has been discussed.

Infectious complications

Our overall results indicate that infectious complications are not different amongst PEG and PRG, with absolute rates of resp. 6% and 7%. Previous reviews or meta-analyses reported infectious rates of 8.4% in PEG (11) and 0.3-7.8% in PRG. The question arises whether the use of prophylactic antibiotics around gastrostomy placement may have influenced the infection rate. Sensitivity analysis by correcting for antibiotic use in the different modalities did not reveal any additional significant difference for infections between PEG and PRG.

Previously, a higher risk of peritonitis was reported in PRG than PEG, with rates of 4 vs. 0 % (RR for PEG 0.24 (95% CI 0.05–1.16)(12, 50). Similarly, in our results, peritonitis was higher in PRG in almost all of the individual studies. Of note is that peritonitis need not to be the result of an intra-abdominal infection, but can be the result of leakage of gastric content and therefore cannot always be prevented by use of antibiotics.

Subgroup analysis

Head and Neck Cancer

Subgroup analysis revealed PEG to be favorable over PRG in HNC patients based on lower rates of procedure related mortality and tube related complications. A limitation of this subgroup analysis is the fact that only three studies could be included, with a total of 349 patients. Sensitivity analysis revealed a significant difference in infectious complications in favor of PEG.

When analyzing the data in more depth, the difference in infectious complications, with absolute rates of 2% in PEG vs. 5% in PRG, mostly entails the severe infections (e.g. peritonitis). This explains the significantly higher rate in the HNC subgroup with PRG. The high rate of peritonitis contributed to the significant difference in procedure related mortality (1% vs 5%) in this subgroup analysis as well. Previous studies reported a lower risk of procedure related mortality after PEG as well (12, 50). The question arises why peritonitis is more common after PRG compared to PEG. In our analysis, only in the subgroup of patients with HNC this difference was significant. This cannot be explained by use of antibiotic prophylaxis; no differences between PEG and PRG were present with regard to antibiotic use in HNC. Rustom et al. described 3 patients with peritonitis (10.7%) in their PRG group, despite antibiotic prophylaxis (38), due to leakage. Several theories regarding higher rate of peritonitis have been proposed. First, the higher number of dislodgements has been pointed out as a possible

cause (15, 45, 47). Secondly also leakage and the fact that the tract is sometimes larger than the tube (45), as well as malposition of the tube during placement (15). Specifically, the use of chemotherapy might also contribute, leading to a suppressed immune response with less effective wound healing and more sensitivity for bacterial wound infections (43). This might therefore explain the fact that only in HNC patients a significant difference is seen.

In our analysis, tube related complications were 4% in PEG and 13% in PRG in HNC patients, and thereby lower than in the overall study population. This might be attributable to the often shorter period of use in HNC patients, where gastrostomies are often used to feed patients during chemoradiotherapy only.

In HNC patients, 30-day mortality was lower than in the overall study population (1% in PEG vs. 7% in PRG). The high number of prophylactic placements in HNC might explain this difference. The general condition prior to placement is better in those patients than in patients with for example MND or post CVA. Unfortunately, we could not perform analyses to assess certain patient characteristics in relation to outcomes on mortality or infections rates. Patient characteristics such as baseline condition could not uniformly be extracted from the included studies. Therefore, no analyses to ascertain predictors or risk factors were executed.

A much feared complication in placement of PEG in HNC is tumor seeding. Currently 49 cases after PEG have been described, whereas only one case has been described in PRG (51-54). This has led to preferential placements of PRGs in patients with HNC. As far as the current analysis is concerned, none of the included studies reported on tumor seeding. One could argue that this apparent lack of tumor seeding could be related to an insufficient length of the follow-up period. When occurring, tumor seeding generally manifests after a mean interval of 7.8 ± 5.2 months (45). Cases have been reported on tumor seeding occurring at a maximum of 13 months after gastrostomy placement (53). No cases are known describing tumor seeding within 3 months after placement. With respect to the studies included in the current analyses, five of the studies in HNC patients had a follow-up that appeared too short for tumor seeding to occur (30-days) (5, 13, 39, 45, 47), however the other five had sufficient duration of follow-up (6-18 months), including 502 patients (4, 12, 15, 35, 38). With this in mind, an extra subgroup analysis might seem valuable, analyzing long-term complications and in particular tumor seeding. However, in our opinion, such subgroup analysis of long-term complications is not possible due to heterogeneity in durations of follow-up resulting in reporting bias. In addition, as no tumor seeding occurred in the studies assessed, it is not possible to perform a separate analysis on this aspect and therefore no firm conclusion can be drawn with respect to the risk of tumor seeding following PEG.

Chapter 2

Stricter patient selection may be more appropriate to prevent tumor seeding. In the included articles, indications were comparable. Clinician's or institutional preference is, on the other hand, a factor of influence. For instance, Grant et al. reported a few clinicians in their institution that choose PRG over PEG for 'risk of tumor seeding', whereas patients with similar tumors were referred for PEG as well by other clinicians (12). McAllister et al. have described a switch to PRG during the course of their study based on local resources, despite finding a higher major complication rate (47). Rustom et al. considered all tumors eligible for PEG with the exception of obstructing oropharyngeal tumors (38). Apart from the risk of tumor seeding, prior surgery and/or chemoradiotherapy may contribute to narrowing the oropharyngeal tract, making PEG positioning more difficult or even impossible. The decision with regard to which mode of gastrostomy to employ in patients with HNC should therefore be based on literature data, local availability and expertise with both techniques and should be personalized for each patient. Such advice is beyond the scope of the present meta-analysis.

Motor Neuron Disease

In MND, PEG and PRG compare favorable for all outcomes, as shown in Figures 2-6. However, only a small number of studies was taken into account, so results from this subgroup analysis ought to be interpreted with caution.

Assignment of patients to either PEG or PRG was often based on clinical and practical considerations (3, 40, 55), or lung function (PRG in case of an FVC <50% (43) or <60% (44). However, baseline differences were all corrected for. In one study, baseline characteristics were similar (41). In most studies, sedation is administered in PEG and not in PRG (40, 41, 45, 47). The largest study however does not mention the use of sedatives (3).

Stavroulakis et al. stated in a meta-analysis amongst MND patients that the difference in 30-day mortality rates were 2.1% higher in PEG (rates of 4-13.3% vs. 4-10% were reported). However, these authors stated that this difference was characterized by a broad 95% CI of -6% to 11%. The meta-analysis by Lim et al. included only three studies; two of low quality and one not comparing PRG and PEG. However, they reported no significant differences in 30-day mortality (17). The discrepancies between findings across meta-analyses can to a large extent be explained by methodological differences.

Limitations

The main limitation of our meta-analysis is that the evidence is based mostly on observational studies. Reporting bias can therefore not fully be excluded. Nevertheless, we have included the currently best available evidence, thereby providing the most accurate estimation of effects. To perform a thorough quality assessment of included studies, two different assessments were used (NOS and ROBINS-I).

The level of evidence appears to be solid considering the low degree of heterogeneity even though only non-randomized data are available.

Conclusion

Overall, no significant differences were found between PEG and PRG with regards to mortality or infectious complications. Patients with PEG had lower risk of tube related complications compared to PRG. This results from higher rate of tube dislocation in the PRG group. Subgroup analysis revealed PEG to be favorable over PRG in head and neck cancer patients based on lower rates of procedure related mortality, infectious, and tube related complications. In MND, no differences were observed.

Considering the small differences in mortality and complications between both techniques, the local experience and availability of the technique should be taken into account in the shared decision process. In order to improve the level of evidence, future studies should be performed in a randomized controlled manner, with uniform definitions for complications and standardized follow-up. The issue of tumor seeding remains to be answered.

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Percutaneous Endoscopic versus Radiologic Gastrostomy for enteral feeding: an analysis on outcomes and complications

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Abstract

Background

Percutaneous Endoscopic Gastrostomy (PEG) and Percutaneous Radiologic Gastrostomy (PRG) are techniques used for long term enteral feeding. Our primary aim was to analyze procedure related and 30-day mortality and complications between PEG and PRG in relation to indications.

Patients and methods

Single center retrospective analysis including all adult patients receiving initial PEG (January 2008 until April 2016) and PRG (January 2010 until April 2016). Outcomes were mortality (procedure related, 30-day), complications (early (≤ 30 days) and late) and success rates.

Results

A total of 760 procedures (469 PRG and 291 PEG) were analyzed. Most common indications were head and neck cancer (HNC), Cerebrovascular Accident (CVA) and Amyotrophic Lateral Sclerosis (ALS). Success rates for placement were 91.2% for PEG and 97.1% for PRG ($p=0.001$). Procedure related mortality was 1.7% in PEG and 0.4% in PRG ($p=0.113$). The 30-day mortality was 10.7% in PEG and 5.1% in PRG ($p=0.481$ after multivariate logistic regression) CVA was associated with higher 30-day mortality, whereas ALS, higher body weight and prophylactic placements in HNC were associated with lower rates.

Tube related complications were less frequent in PEG, both early (2.7% vs. 26.4%, $p<0.001$) and late (8.6% vs. 31.5%, $p<0.001$). The percentage of major complications and infections did not differ.

Conclusion

With respect to procedure related and 30-day mortality, PEG and PRG compare equally. PRG had a higher procedural success rate. Tube related complications and pain are less frequent after PEG compared to PRG. The choice for either PEG or PRG therefore should primarily be based on local facilities and expertise.

Introduction

Gastrostomy is the method of choice for enteral feeding that is expected to last longer than four weeks (medium- and long term enteral feeding)(1, 2). Available gastrostomy techniques include Percutaneous Endoscopic Gastrostomy (PEG) and Percutaneous Radiologic Gastrostomy (PRG). PEG was developed in 1980 by Gauderer et al. Shortly afterwards, Preshaw et al. developed a radiologic alternative (3); PRG, also called Fluoroscopy Guided Gastrostomy (FPG) or Radiologically Inserted Gastrostomy (RIG). Both techniques are preferred over surgical gastrostomy due to lower morbidity rates (4-6).

Main indications for gastrostomy placement include dysphagia or swallowing dysfunction, caused by neurological disorders (Cerebral Vascular Accidents (CVA), Amyotrophic Lateral Sclerosis (ALS)), malignancies (esophageal, head and neck cancer (HNC)), malnutrition and motility disturbances of the upper gastrointestinal tract (4, 7). The group of patients receiving a PRG or PEG is characterized by poor condition due to malnutrition and underlying disease. Therefore, complications of PEG or PRG placement are likely to have a major impact on prognosis and outcome.

Consensus on which technique/route should be preferred as access for enteral feeding, with respect to safety, success rates, complications and availability, has not yet been reached.

Previous reports on this topic are of limited value due to small sample sizes and high risk of confounding and selection bias (8-14). These studies suggest that both techniques are comparable in terms of morbidity and mortality (8, 15, 16). Dislocation, obstruction and other tube related complications appear to occur more often in PRG. Peristomal infections more frequently occur in PEG. For this reason antibiotic prophylaxis is now recommended to lower this risk, resulting in a risk reduction from 24.2% to 8.4% (17). Because the tube is not pulled through the oropharynx cavity in PRG, transfer of oropharyngeal microbiota more distally is avoided. The risk of infection is therefore assumed to be lower (around 0.3-7% without antibiotics (18)) and routine administration of antibiotics in PRG procedures is not recommended.

An advantage of PRG is that the procedure is generally performed without sedation (in contrast to PEG) and that PRG can also be placed in cases of esophageal stenosis or (malignant) esophageal/oropharyngeal obstruction (19). Tumor seeding to the stoma site is a feared complication of PEG, with currently 49 reported cases in the literature, whereas one case of tumor seeding has been described after PRG (20-22).

Chapter 3

In our center both PEG and PRG are available and used on a regular basis. Choice for one of the two techniques is empirical. Our primary aim was to retrospectively analyze data from our center with respect to procedure related and 30-day mortality and complications of PEG and PRG procedures in relation to indications and to compare PEG and PRG results. These data may help to better predict which technique may serve as best option for an individual patient.

Methods

Data of all adult patients receiving initial PRG (January 2010 until April 2016) and PEG or PEG-J (January 2008 until April 2016) placement at the Maastricht University Medical Center, a tertiary referral center, were retrospectively analyzed. Patients with PEG placements with additional duodenal/jejunal extension were included in the PEG group. Data from PRGs prior to 2010 were not available. PEGs from 2008 and 2009 were included to create a sample size comparable to PRG. In case of incomplete follow-up data, patients were excluded from the analysis.

Procedure

Prior to gastrostomy placement, oral anticoagulants were temporarily stopped (preferable INR < 1.5 in case of vitamin K antagonists) for 2-5 days, as well as thienopyridines (for 5-7 days). Use of acetylsalicylic acid was allowed.

PEG

Conscious sedation using midazolam (low dose, mean 2.5mg) and a fast acting opioid (pethidine or fentanyl) was administered. Oral amoxicillin/clavulanic acid 1200mg was given 30 min before the procedure (in case of allergy, a substitute was given). PEG (Freka PEG, 15Fr, Fresenius Kabi AG, Bad Homburg, Germany) placement was performed according to the standard Pull-method as first performed by Gauderer et al 23. In several cases (n=26), a jejunal extension tube was placed through the PEG tube, and pulled distally from the papilla of Vater with a grasping forceps. Afterwards, patients were observed for at least one hour at the day care unit. Immediately after placement, water was administered through the tube. Feeding was started the next day.

PRG

PRG placement was performed using a Wills-Oglesby Percutaneous Gastrostomy Set (12Fr, Cook, Bloomington, IN 47402-4195 U.S.A.). Neither standard prophylactic antibiotics nor sedatives were given. Before the procedure, using ultrasound, the location of the stomach was checked as well as any possible interposing organs (left liver lobe, (transverse) colon, small bowel). After intravenous injection of 20 mg of buscopan, the stomach was inflated using a gastronasal tube placed inside the stomach before the procedure. After local anesthesia with 20-30ml of 1% lidocaine, the stomach was punctured under fluoroscopic (and sometimes ultrasound) guidance to place the anchors. In total three anchors were placed in a triangular orientation. Intragastric position of the needle was confirmed using a small amount of contrast material. After fixation of the three anchors, the stomach was punctured centrally between the anchors, and a guidewire inserted. After dilatation of the tract, the gastric tube was placed over the wire. The day after placement, saline fluids were administered through the tube for 3-6 hours. Feeding was started thereafter and the patient was discharged. Ten

to fourteen days after the procedure, patients returned to the radiology department to remove the anchors.

Data collection

Baseline data collected from medical records were gender, age, BMI before tube placement, weight loss before gastrostomy placement, indication for tube placement, significant comorbidities (chronic cardiac, pulmonary, kidney, gastrointestinal and liver diseases, malignancies and diabetes mellitus (DM)).

Retrospectively, all patient files, including endoscopic and radiologic reports, were reviewed to ascertain whether any complications had occurred during follow up (maximum six years), including death. In- and exclusion for PEG and PRG are stated in Figure 1.

Outcome measures

The primary outcome measure was mortality (30-day and procedure related (defined as mortality occurring due to a complication of the procedure)), secondary outcomes were the occurrence of complications, early (<30 days) and late, scored as minor or major (4, 7), and procedure success rates. Complications were analyzed according to the international CIRSE, AGA and ESPEN classification (4, 7, 23), and divided into early and late complications (≤ 30 days, and > 30 days), as well as severity: minor (requiring conservative treatment) or major. Infection was classified as erythema, pain, and/or purulent discharge, requiring antibiotic treatment (as diagnosed by expert clinical opinion). Dislocation, obstruction, leakage and tube/balloon defects were reported combined, as "tube-related complications". PRG tubes were preventively replaced after 3-6 months, through the existing fistula channel. These scheduled replacements were not scored as complications. PEG tubes or PEG tubes with a jejunal extension (PEG-j) tubes were not routinely replaced.

Statistical analysis

Data analysis was performed using SPSS for Windows, version 23 (IBM Corporation). Data are presented as frequencies for categorical variables, and as mean $\pm$ standard deviation (SD) for continuous variables. Indications, diagnosis and comorbidities were recoded into dichotomous variables. Normal distribution was tested for continuous variables. Chi²-tests were used to compare categorical data and t-tests for continuous data. In univariate logistic regression, Chi²-test or Fisher's exact test (in case of small samples) was used to identify predictors or risk factors of complications and mortality, whereas the Mann Whitney U test was used for continuous variables. All statistical tests were two-sided, with a significance level of 0.05. Multivariate logistic regression was performed to determine predictors of complications in case binary logistic regression revealed significant factors. These factors

were introduced in the multivariate models in a stepwise way. Multicollinearity and interactions in multivariate analysis were tested and corrected for and adjusted ORs are shown. Odds ratios were calculated for PEG compared to PRG.

Ethical considerations

This study was approved by the Medical Research Ethics Committee of the Maastricht University Medical Center. The study was conducted according to the Dutch Codes of Conduct.

Results

In total 856 (502 PRG, 354 PEG) patient files matching our search criteria were found.

The patient inclusion flow chart is presented in Figure 1. The difference in procedural success rates: 91.2% for PEG (291/319) and 97.1% for PRG (n=469/483) was statistically significant ($p=0.001$). Various reasons account for failure of placement. In PEG, these included inability to obtain transillumination (41% of failed cases, $n=14$), stenosis (26%, $n=9$), an intrathoracic position of the stomach (15%, $n=5$). In addition, PEG placement was not performed due to presence of high-risk factors such as ascites (15%, $n=5$) or inability of a patient to adequately open his mouth (3%, $n=1$).

The inability to puncture the stomach was the most frequent factor for failure of PRG placement ($n=8$, 57% of failed cases). This was either related to previous surgery (Billroth II stomach, $n=3$, 21%), or was due to a too painful procedure (21%, $n=3$). In case of PEG failure, PRG placement was successfully performed in 8 cases. PEG after PRG failure was successfully performed in 3 patients.

A total of 760 successful procedures (469 PRG and 291 PEG) were included in the analysis (62.9% male, mean age 62.8yrs [SD 12.64]). Baseline characteristics are shown in Table 1.

Figure 1. Flow chart of all PEG and PRG patients, in- and exclusion

* Not first PEG/PRG: Multiple gastrostomy procedures

Unsuccessful procedure: due to absence of transillumination, intrathoracic position of stomach, colon interposition

High risk: presence of ascites or estimated high risk for tumor seeding

Table 1. Baseline characteristics of patients who underwent PEG or PRG at the Maastricht UMC between 2008 and 2016

Parameters	PEG N (%*) (total n=291)	PRG N (%*) (total n=469)	p-value
Male	173 (59,5%)	305 (65%)	0.208
Age (yrs)			
Range	20-90	22-72	
Mean [SD]	63,38 [10,97]	62,41 [14,94]	0.306
Weight loss before (kg)			
Range	0-42kg	0-34kg	
Mean [SD]	4,17 [6,281]	4,99 [6,364]	0.023
BMI before (kg/m ²)			
Mean [SD]	23,61 [13,09]	22,19 [4,60]	0.120
Diagnosis			
<i>Amyotrophic Lateral Sclerosis (ALS)</i>	8 (2.7)	46 (9.8)	<0.001
<i>Cerebrovascular accident (CVA)</i>	40 (13.7)	10 (2.1)	<0.001
<i>Cystic Fibrosis</i>	4 (1.4)	2 (0.4)	0.210
<i>Gastrointestinal motility disorder</i>	19 (6.5)	0 (0)	<0.001
<i>Head/neck malignancy (Total, including prophylactic)</i>	113 (38.8)	328 (69.9)	<0.001
<i>Head/neck malignancy</i>	66 (22.6)	294(62.6)	<0.001
<i>(Prophylactic placements only)</i>			
<i>Long-term enteral feeding, disorder not specified</i>	21 (6.7)	9 (1.9)	0.001
<i>Malignancy not in Head/neck region</i>	21 (7.2)	18 (3.8)	0.398
<i>Muscular disease</i>	11 (3.8)	15 (3.2)	0.668
<i>Neurological disease, (including multiple sclerosis, Parkinson's disease)</i>	41 (14)	13 (2.7)	<0.001
<i>Post-surgical/traumatic swallowing dysfunction</i>	13 (4.5)	4 (0.9)	0.001
Comorbidities	8 (2.7)	6 (1.3)	0.143
<i>Severe pulmonary disease</i>	1 (0.3)	1 (0.2)	1
<i>Heart failure</i>	23 (7.9)	19 (4.1)	0.024
<i>Diabetes Mellitus</i>	3 (1.0)	3 (0.6)	0.680
<i>Immune suppressives</i>	3 (1.0)	4 (0.9)	1
<i>Recent CVA</i>	1 (0.3)	0 (0)	0.383
<i>Hemodialysis</i>	10 (3.4)	41 (8.7)	0.004
<i>≥2 primary malignancies</i>	1 (0.3)	7 (1.5)	0.163
<i>Recurrent malignancy</i>	1 (0.3)	1 (0.2)	1
<i>Liver cirrhosis</i>	6 (2.1)	3 (0.6)	0.078

Parameters	PEG N (%*) (total n=291)	PRG N (%*) (total n=469)	p-value
<i>Infection around placement</i>	5 (1.7)	1 (0.2)	0.033
<i>Aspiration pneumonia before placement</i>	8 (2.7)	4 (0.9)	0.042
<i>Cognitive disorder</i>	3 (1.0)	2 (0.4)	0.377
<i>Parkinson's disease</i>	6 (2.1)	3 (0.6)	0.078
<i>Severe Vascular disease</i>	0 (0)	1 (0.2)	1
<i>Von Willebrand disease</i>	2 (0.7)	1 (0.2)	0.562
<i>Severe esophageal/stomach ulcer</i>	0 (0)	1 (0.2)	1
<i>Plummer Vinson syndrome</i>	210 (72.2)	371 (79.1)	
<i>None</i>			

*total 99.6 -99.9% due to round off

30-day mortality

The 30-day mortality was significantly different between both procedures, with a mortality rate of 10.7% in PEG group vs. 5.1% in the PRG group ($p=0.005$, OR 2.214 [1.263-3.879]). After correction for age, gender, weight, diagnosis and comorbidities in a multivariate logistic regression model, this difference between PEG and PRG was no longer significant ($p=0.481$, OR 0.771 [0.374-1.590]). Presence of CVA (OR 5.190 [2.139-12.597]) was associated with higher 30-day mortality. ALS (OR 0.231 [0.104-0.518]), a higher weight before placement (OR 1.002 [1.001-1.003]) and prophylactic placements in HNC were associated with lower 30-day mortality (OR 0.307 [0.212-0.444]).

Procedure related mortality

Procedure related mortality was 1.7% ($n=5$) in PEG and 0.4% ($n=2$) in PRG ($p=0.113$). Four PEG patients died due to aspiration pneumonia, one patient died from a massive gastric bleeding. Indications for PEG in these patients were HNC ($n=3$), and CVA ($n=2$). Two patients with aspiration pneumonia had experienced recurrent aspiration before PEG placement (one probably due to a tracheoesophageal fistula), two were in poor condition after a major CVA.

Both deceased patients in the PRG group died from aspiration pneumonia and had severe comorbidities (liver cirrhosis resp. vascular dementia). One of them had been treated for aspiration pneumonia prior to gastrostomy.

Complications

Tube patency and tube related complications

The overall complication rates are shown in Table 2. Tube related complications (including dislocation, obstruction, leak and tube defects) were less frequent in PEG than PRG, both within 30 days (2.7% vs. 26.4% of patients, $p < 0.001$ and after 30 days (8.6% vs. 31.5%, $p < 0.001$). Adjusted ORs after multivariate correction for baseline differences for PEG vs. PRG can be found in Table 3, overall adjusted OR were 0.061 [0.026-0.139] for early tube related complications, and 0.252 [0.155-0.411] for late tube related complications. No multicollinearity or interactions were found.

In some patients, tube related complications occurred more than once. The total number of tube related complications are shown in Table 4. In the PRG group, more than one tube related complication occurred in 46 patients (9.8%), in the PEG group in 17 patients (5.8%, all PEG-j patients).

Table 2. Complications (total no. of pts)

Early Complications (≤30 days)				
	PEG n=291 (%)	PRG n=469 (%)	p-value	Significant OR [95%CI]
Peristomal irritation (erythema)	4 (1.3)*	34 (7.2)*	<0.001	0.133[0.041-0.438]
Peristomal infection	5 (1.7)*	7 (1.5)*	0.808	
Pain	11 (3.8)	43 (9.2)	0.005	0.389[0.197-0.768]
<i>Requiring conservative treatment</i>	1 (0.3)	1 (0.2)	1	
<i>Requiring removal</i>				
Tube related complications°	8 (2.7)	124 (26.4)	<0.001	0.079[0.038-0.164]
<i>Replacement through existing channel</i>	7 (2.4)	115(24.5)	<0.001	0.083[0.038-0.180]
<i>Requiring new tube procedure</i>	1 (0.3)	9 (1.9)	0.064	
Bleeding	6 (2.0)	6 (1.3)	0.400	
Peritonitis	0 (0)	2 (0.4)	0.527	
Abscess	0 (0)	2 (0.4)	0.527	
Aspiration pneumonia	6 (2.1)	4 (0.9)	0.155	
Late complications (>30 days)				
	PEG n=291 (%)	PRG n=469 (%)	p-value	Significant OR [95%CI]
Skin deterioration /granuloma	11 (3.8)	0*	0.005	18.905[2.486-143.737]
<i>Requiring conservative treatment</i>	3 (1)	0*	0.056	
<i>Requiring removal</i>				
Pain	1 (0.3)	5 (1.1)	0.415	
<i>Requiring conservative treatment</i>	2 (0.7)	1 (0.2)	0.562	
<i>Requiring removal</i>				
Tube related complications° (no. pts)	23 (7.9)	139 (29.6)	<0.001	0.236[0.151-0.368]
<i>Replacement through existing channel</i>	19 (6.5)	122 (26)	<0.001	0.199[0.119-0.330]
<i>Requiring new tube procedure</i>	6 (2.0)	26 (5.5)	0.026	0.359[0.146-0.882]
Abscess	1 (0.3)	2 (0.4)	1	
Infection	4 (1.4)	5 (1.1)	0.702	
Bleeding (<i>requiring laparotomy</i>)	0 (0.0)	1 (0.2)	1	
Perforation (<i>requiring laparotomy</i>)	0 (0)	1 (0.2)	1	
Tumor seeding	0 (0)	1 (0.2)	1	
Buried bumper	4 (1.4)	2 (0.4)	0.21	

° including dislocation, leak, blockage

*probably underreporting

Other complications

Early major complications (including peritonitis, abscess, buried bumper, pneumonia) occurred in 3.4% of patients in PEG vs. 1.8% in PRG ($p=0.193$). Late major complication rates were 5.4% in PEG vs. 7.1% ($p=0.121$) in PRG.

We observed one case of tumor seeding (HNC) occurring after a PRG procedure. A significantly higher rate of post-procedural pain was found in PRG (9.2% vs. 3.8% in PEG). This was adequately treated with oral analgesics after the procedure.

Late skin deterioration (e.g. redness, mild granuloma formation) occurred more frequently in PEG patients (3.8% vs. 0% in PRG, $p=0.005$). Removal of the PEG was required in three patients due to skin deterioration.

Table 3. Predictive factors for complications and mortality (OR for PEG vs. PRG)

	Adjusted OR [95%CI]	p-value
Early complications		
Tube related complications (total)	0.061[0.026-0.139]	<0.001
HNC	0.120[0.081-0.178]	<0.001
ALS	0.053[0.023-0.122]	<0.001
Esophageal malignancy	0.014[0.002-0.105]	<0.001
≥2 primary malignancies	0.393[0.170-0.911]	0.030
Tube related complications (minor)	0.061[0.026-0.139]	<0.001
HNC	0.121[0.082-0.179]	<0.001
ALS	0.055[0.024-0.126]	<0.001
Esophageal malignancy	0.014[0.002-0.108]	<0.001
≥2 primary malignancies	0.395[0.171-0.910]	0.029
Pain (minor)	0.345[0.161-0.739]	0.006
HNC	0.142[0.0750-0.271]	<0.001
ALS	0.074[0.033-0.151]	<0.001
Esophageal malignancy	0.020[0.003-0.151]	<0.001
≥2 primary malignancies	0.323[0.146-0.713]	0.005
Infection (minor)	0.099[0.028-0.352]	<0.001
HNC	0.156[0.106-0.229]	<0.001
ALS	0.076[0.033-0.173]	<0.001
Esophageal malignancy	0.019[0.002-0.142]	<0.001
≥2 primary malignancies	0.284[0.126-0.638]	0.002

	Adjusted OR [95%CI]	p-value
Late complications		
Granuloma/skin deterioration	23.028[2.364-22.275]	0.007
HNC	0.164[0.112-0.241]	<0.001
ALS	0.081[0.036-0.183]	<0.001
Esophageal malignancy	0.021[0.003-0.158]	<0.001
≥2 primary malignancies	0.261[0.114-0.599]	0.002
Tube related complications (total)	0.252[0.155-0.411]*	<0.001
HNC	0.151[0.077-0.294]	<0.001
ALS	0.124[0.051-0.301]	<0.001
Esophageal malignancy	0.020[0.003-0.154]	<0.001
≥2 primary malignancies	0.347[0.151-0.795]	0.012
Tube related complications (minor)	0.198[0.113-0.347]*	<0.001
HNC	0.135[0.070-0.262]	<0.001
ALS	0.112[0.046-0.271]	<0.001
Esophageal malignancy	0.019[0.002-0.146]	<0.001
≥2 primary malignancies	0.331[0.148-0.742]	0.007
Tube related complications (major)	0.404[0.154-1.059]*	0.065
HNC	0.152[0.080-0.287]	<0.001
ALS	0.078[0.034-0.175]	<0.001
Esophageal malignancy	0.021[0.003-0.161]	<0.001
≥2 primary malignancies	0.346[0.157-0.759]	0.008

*after adjusting for multicollinearity and interactions

Table 4. Total no. of tube related complications

Early	PEG n=291 (%)	PRG n=469 (%)	p-value
<i>Minor (replacement through old canal)</i>	7 (2.4)	127 (27.1)	<0.001
<i>Dislocation</i>	4 (1.4)	107 (22.8)	0.231
<i>Leak</i>	2 (0.7)	8 (1.7)	0.231
<i>Obstruction</i>	1 (0.3)	11 (2.3)	1
<i>Balloon defect</i>	0	1 (0.2)	0.064
<i>Major (completely new tube)</i>	1 (0.3)	9 (1.9)	0.163
<i>Dislocation</i>	1 (0.3)	7 (1.5)	0.527
<i>Leak</i>	0	2 (0.4)	

Late	PEG n=291 (%)	PRG n=469 (%)	p-value
<i>Minor (replacement through old canal)</i>	22 (7.5)	146 (31.1)	<0.001
<i>Dislocation</i>	10 (3.4)	107 (22.8)	0.895
<i>Leak</i>	7 (2.4)	12 (2.6)	0.177
<i>Obstruction</i>	5 (1.7)	19 (4)	0.231
<i>Balloon defect</i>	0	8 (1.7)	0.036
<i>Major (completely new tube)</i>	6 (2.0)	26 (5.5)	0.383
<i>Dislocation</i>	4 (1.4)	26 (5.5)	0.383
<i>Leak</i>	1 (0.3)	0	
<i>Obstruction</i>	1 (0.3)	0	

Discussion

Our study, involving 760 patients receiving either PEG or PRG as route for nutritional support, showed a higher procedural success rate for PRG compared to PEG. The overall 30-day mortality rate was significantly higher in the PEG group when compared to the PRG group. However, when corrected for age, gender, weight, diagnosis and comorbidities, this difference was no longer significant. No differences in procedure related mortality and complications were noted between both methods used.

30-day mortality

In literature, the reported 30-day mortality rates in PEG and PRG are comparable (8, 15, 16). In our current analysis, multivariate logistic regression revealed no significant difference between PEG and PRG related 30-day mortality. It appears that the underlying diseases and condition of the patient, and not the procedure are predictive factors. Of particular note is that a significantly higher number of patients with CVA received PEG whereas a PRG was placed in relatively high number of HNC and ALS patients which also might explain the difference seen in the uncorrected analysis. Patients with prophylactic placement for HNC, ALS, and a higher BMI before placement had a lower risk of 30-day mortality. The patients with prophylactic placement had often been treated with curative intentions for their malignancies. Prognosis across the different patient groups undergoing gastrostomy also impacts 30-day mortality rates following gastrostomy placement. In ALS, rates of 3-15% are reported for both procedures (24-27), whereas median survival for MND in general is 32 months following diagnosis (28). In HNC, rates of 0-1% in PEG and 0-4% in PRG are reported (19, 29, 30), with a 5-year survival for all forms and stages of HNC being 50% (31). In CVA, which was predictive for higher 30-day mortality in our study, rates of 11-14% 30-day mortality have been reported (32). Abuksis et al. reported a 30-day mortality of 72% after PEG placement in hospitalized patients in general (33). Whereas higher BMI was protective for 30-day mortality, age and comorbidities (such as DM, cirrhosis, cancer, COPD) were not risk factors for 30-day mortality in our analysis. Previous literature however reported all these factors as predictive factors for 30-day mortality (34-38).

Procedure related mortality

Procedure-related mortality was not significantly different between PRG and PEG. Our findings are in contrast to some previous studies, in which a higher procedure related mortality after PRG vs. PEG has been reported with rates of 1% in PEG vs. 2-7% in PRG (19, 30, 39). On the other hand, our data are in line with several others reports with mortality rates of 0-2% both in PEG and PRG, not being different from each other (8, 25, 40, 41).

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The question remains whether or not aspiration pneumonia within 7 days after gastrostomy placement is attributable to the procedure itself or is also resulting from other precipitating factors that provide a higher risk for aspiration in general. In other words, assuming that aspiration pneumonia was already present at the time of gastrostomy. Many patients experienced recurrent aspirations prior to placement of a gastrostomy. In our group, this was the case with 33 patients (4.3%) in total. Of the patients with procedure related mortality with aspiration, this was 50%.

The risk of periprocedural aspiration is considered to be higher after use of sedatives. As a consequence, the risk of aspiration is supposed to be lower in PRG as no sedatives are used (42, 43). However, our analysis did not show significant differences. Higher pneumonia rates have also been reported after PRG (41). Special concern exists for ALS patients, in whom respiratory function often is impaired. Moreover, masseter muscle spasms might occur as well, in which the small insufflation tube in PRG can mostly be introduced, contrary to the endoscope in PEG (24). In our hospital, PRG is first choice of treatment in ALS for the above stated reasons. A recent study by our group analyzing an ALS subgroup showed that conscious sedation in ALS is safe, even in patients with moderate pulmonary dysfunction (44).

Tube related complications

Early tube related complications (dislocation, leak, blockage) were more likely to occur in PRG than PEG. This is probably due to smaller diameter of the PRG tubes, 12Fr. versus 15Fr. in PEG, and the less solid fixation (with a locked pigtail) versus a more solid flange in PEG. The higher rate found in PRG (26.4% early, 29.6% late) is comparable to previous literature, reporting on rates between 21-40% (15, 30, 45, 46). Tube dislocation appeared to be a risk factor for peritonitis due to leakage of gastric contents to the peritoneal cavity (15, 29, 39) This however could not be demonstrated in our study. The jejunal extension in PEG-J is known to dislocate more often than regular PEG, up to 27-36%, but other complication rates are comparable with PEG (47-49).

Infectious complications

In line with previous reports, low rates of minor and major infections were observed. Early minor infection rates were 1.7% in PEG, 1.5% in PRG(27,52). However, higher (minor) infection rates of 8-15% in PEG (4, 40) and 2-22% in PRG (16, 19, 25) have also been reported. We cannot exclude that minor infections have been underreported, as our center is a tertiary referral center. Minor problems may have been treated at local hospitals or by general practitioners.

Other complications

Major complications did not differ amongst the two groups. Complication rates found in our study largely compare to literature data (19, 29, 43, 46). Post-procedural pain at the gastrostomy site is common, probably due to gastropexy (26, 50). Previous studies showed pain in 9.5% after PRG, which is in line with our current findings, showing minor pain in 9.2% shortly after PRG placement (compared to 3.8% in PEG). Of note is that pain post-PRG is generally easily treated with a short course of oral analgesics. Skin deterioration might also be prone to underreporting. According to our findings, this complication occurs more often in PEG than PRG. Not all patients consider this a problem, or it is not recognized. Literature rates therefore vary from 0-12% in PEG and 2.3-20% in PRG (15, 25, 40).

Tumor seeding

At our institution, a PRG procedure is preferred over a PEG procedure for patients with oropharyngeal tumors. It may well be that the low number of tumor seeding in our study is related to avoidance of PEG placement as only 8 PEG patients with an oropharyngeal tumor received the PEG before surgery. Remarkably, tumor seeding occurred in one patient after PRG which has been reported only once in the literature (22). Tumor seeding is considered to occur by transposition of tumor cells to the stomal site after pulling the gastrostomy tube alongside the tumor. Hematogenous spread of tumor cells might be another explanation. Adhesion of tumor cells at a gastrointestinal wound site after desquamation of tumor cells with subsequent swallowing (20, 21, 51) has also been proposed.

Despite our remarkable finding, the risk of tumor seeding in oropharyngeal tumors has been shown to be higher with PEG than PRG, which is supported by numerous case reports (20-22, 52). For other HNC tumors, the risk is comparable based on literature (19, 29, 30) and data presented here.

Limitations

The current study has several limitations. First, due to the retrospective nature of the analysis, assignment to groups was empirical, based on clinical judgment and practical considerations, instead of randomization, thereby rendering the patient groups PEG vs. PRG quite heterogeneous. We have included all patients in the specified periods and corrected all baseline confounders by multivariate logistic regression to minimize risk of bias. Missing data with regard to weight loss prior to placement and BMI, were mostly encountered in patients with PEG from the years 2008-2009. Secondly, the inclusion period was longer for PEG, to reach comparable numbers. Baseline characteristics of 2008 and 2009 did not significantly differ from those of 2010 until 2016. Therefore, we do not expect that the longer inclusion period will have influenced the results.

Thirdly, some patients received a PRG after PEG failure and vice versa. We do not expect this deviation from the intended intervention to influence outcomes, because we only assessed outcomes of

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successful procedures. Fourthly, mortality and complication rates are dependent on expertise of the radiologists/endoscopists and their supporting team. Local preference for PRG or PEG is dependent of availability, expertise and teamwork. In an ideal setting both techniques are available and can be used based on patient and team preference.

Finally, costs of both procedures may influence decision making. However, a precise estimation of costs is difficult. Not only procedural costs, but also follow-up, re-interventions and complications should all be taken into account. The difficulty is emphasized by previous estimations, ranging from \$591-2400 for PEG and \$406-4500 for PRG (2, 40, 43).

Advice for daily practice

Considering the significant 30-day mortality, neither PEG nor PRG placement should be considered in patients with a very short life expectancy and a very poor condition (e.g. after a major CVA)(53). Nasogastric or nasoduodenal feeding is an acceptable and relatively safe alternative (54) with no higher aspiration rates than in case of gastrostomy.

In patients requiring prolonged enteral feeding both PEG and PRG should be considered, taking into account local practice and existing expertise. The process of clinical decision making should take into account aspects of the underlying disease and of a team of experienced gastroenterologists and interventional radiologists. We advocate for a thorough selection for each individual patient, taking into account the risks and burdens of a gastrostomy and the type of gastrostomy. A multidisciplinary approach combined with a dedicated outpatient clinic (for assessment of the patient and providing information) is highly recommended.

Conclusion

With respect to procedure related and 30-day mortality, PEG and PRG compare equally. The underlying disease appears to be the most important predictive factor of mortality. PRG has a higher procedural success rate and placement even is possible in case of a stenotic or narrow esophagus. Tube related complications and pain are less frequent after PEG compared to PRG. These complications are generally easily managed. The choice for PEG or PRG therefore should primarily be based on local facilities and expertise.

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3

COMPLICATIONS IN PEG

Antibacterial gauzes are effective in preventing infections after Percutaneous Endoscopic Gastrostomy placement.

A retrospective analysis

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Abstract

Background

The most common complication after percutaneous endoscopic gastrostomy (PEG) placement is peristomal wound infection (up to 40% without antibiotic prophylaxis). Single-dose parenteral prophylactic antibiotics as advised by current guidelines decrease the infection rate to 9–15%. We assume a prolonged effect of local antibiotic treatment with antibacterial gauzes. This study is the first to describe the effect of antibacterial gauzes in preventing infections in PEG without the use of antibiotics.

Patients and methods

A retrospective data analysis was carried out of all patients with PEG insertion between January 2009 and October 2014 in the Catharina Hospital Eindhoven. Data include placement and the period of the first 2 weeks after PEG placement, and long-term follow-up. All patients received a locally applied antibacterial gauze (polyhexamethylene biguanide) immediately following PEG insertion for 3 days. No other antibiotics were administered. The main outcomes were wound infection, peritonitis, and necrotizing fasciitis; secondary outcomes included other complications.

Results

A total of 331 patients with only antibacterial gauzes were analyzed. The total number of infections 2 weeks after PEG insertion was 9.4%, including 8.2% minor and 1.2% major infections (peritonitis). No wound infection related mortality or bacterial resistance was found. Costs are five times lower than antibiotics, and gauzes are more practical and patient friendly for use.

Conclusion

Retrospectively, antibacterial gauzes are at least comparable with literature data on parenteral antibiotics in preventing peristomal wound infection after PEG placement, with an infection rate of 9.4%. Rates of other complications found in this study were comparable with current literature data.

Introduction

Percutaneous endoscopic gastrostomy (PEG) is the current method of choice in enteral feeding that is expected to last at least 4 weeks (medium-term and long-term enteral feeding)(1, 2). The main indication for PEG placement is dysphagia, caused by for example neurologic disorders (cerebrovascular incidents, Amyotrophic Lateral Sclerosis), cancer (esophageal, head and neck cancer), malnutrition, as well as admission of medication (Parkinson disease: jejunal admission of duodopa).

The select group of patients receiving a PEG are mostly in a vulnerable condition before placement. However, PEG is a minimally invasive procedure and is commonly used in current practice. A feeding tube is placed endoscopically in the stomach wall throughout the abdominal wall to provide an enteral feeding canal. PEG placement is safe and well tolerated in the majority of patients. However, complications may occur; the reported rates vary depending on patient selection and different methods of scaling. The overall rate of complications is found to be between 4.9 and 40% (1, 3, 4). Most of the reported complications are minor, e.g. wound infection or minor bleeding; major complications such as peritonitis, bleeding, perforation, necrotizing fasciitis, and death occur at rates reported at 0.4 to 5% (3, 5) (Table 1).

Peristomal wound infection occurs at rates between 8 and 47% (6, 7); the most recent systematic review (2013) reported a percentage of 9.4% on administration of intravenous antibiotics compared with 24.2% on administration of placebo or nothing (8). The ESPEN guideline reports a percentage of 15% (1). Other studies found similar rates (7); however, not all criteria used for infection and antibiotics used are comparable. In case of wound infection, culture of the insertion site is not proven to be useful in general. Removal of the PEG is not necessary if a proper antibiotic response is observed (3, 5). Peritonitis might be caused by a severe wound infection. However, sometimes, it is caused by a leakage of gastric contents, which should be excluded with radiologic imaging. In case of peritonitis, tube feeding must be stopped and antibiotics should be started. Generally, a first-generation cephalosporin or quinolone is effective (5).

A necrotizing fasciitis after PEG placement is rare. Signs of this severe complication are edema and erythema with bullae locally, with a progressive course and signs of severe infection systemically. The PEG needs to be removed immediately and antibiotic treatment is required.

The current guidelines do not completely agree on the use of prophylactic antibiotics in PEG placement. The European (ESPEN) guideline states that the use of antibiotic prophylaxis is not mandatory in experienced hands under established hygienic conditions, although it is recommended in cases of doubt or less experience (1). The American Society for Gastrointestinal Endoscopy, however,

highly recommends a single administration of parenteral cefazolin (2 g) 30 min before starting the procedure (3, 9). Use of other cephalosporins and penicillins has been reported in many trials (10-12); however, cefazolin has been recommended in a meta-analysis. It has been reported that this is not necessary in patients already receiving appropriate antibiotics around the time of the procedure (3).

Methicillin-resistant *Staphylococcus aureus* (MRSA) is commonly found in infected PEG sites. Some studies found beneficial results in prescreening for MRSA (13) and nasopharyngeal decontamination in reducing the wound infection rate (5, 14). However, this is not a strong recommendation as yet.

Antibiotic resistance, for example, in case of MRSA, is leading to increasing concern (14). The use of antibiotics is therefore minimized in our hospital. Besides, the use of prophylactic antibiotics is relatively expensive and not patient friendly if administered intravenously.

Table 1. Incidence of complications after PEG placement (2, 6, 15-17)

Early complications (within 14 days)	Incidence	Late complications (after 14 days)	Incidence
Minor peristomal infection	18-30% (without antibiotic prophylaxis) 8-15% with prophylaxis	Deterioration of skin	2.4%
Bleeding	1-2.5%	Buried bumper syndrome	0.3-2.4%
Peristomal leak	1-2%	Stomach herniation	Very rare
Ileus and gastroparesis	1-2%	Tumor implantation at PEG site	Mainly in oropharyngeal tumors, <1% in that group
Dislocation of PEG tube	1.6-4.4%	Colocutaneous fistula	Very rare
Peritonitis	1-2.3%	Gastro-colo-cutaneous fistula	Very rare
Gastric outlet obstruction	<1%	Peristomal pain	Unknown
Necrotizing fasciitis	<1%	Colon perforation	12 case reports
Aspiration	0.3-1%		
Liver / splenic injury	Very rare		
Pneumoperitoneum	56%, persistent; very rare		
Clogged PEG tube	3.5-35%		
PEG site herniation	1 case known		

Since 2009, a novel approach toward the prevention of infectious complications around PEG insertion is being used in our department: antibacterial gauzes (Excilon PHMB; Covidien, Mansfield, Massachusetts, USA) are used instead of prophylactic intravenous antibiotics. The gauze method has been the only method used in PEG insertion from 2009; the conventional method has not been used since. The gauzes are applied locally at the insertion site, directly after PEG insertion, and left for 3 days. These gauzes are effective for 7 days. In this manner, the gauzes confer longer protection against peristomal wound infection than a single dose of intravenous antibiotics. By the mechanism of action, bacterial resistance is not to be expected (18).

Objectives

The aim of this study was to retrospectively evaluate the peristomal infectious complications of PEG placement in the Catharina Hospital Eindhoven, the Netherlands, from January 2009 until October 2014. We hypothesize a comparable rate of infections with antibacterial gauzes compared with the literature.

Methods

Study design

A retrospective study was carried out to evaluate the prophylactic effect of an antibacterial gauze on peristomal infections after PEG insertion. All other complications were also assessed in the short term (2 weeks) after PEG and in the long term.

Setting and participants

All patients who underwent PEG, PEG-J (PEG with jejunum extension), or PEJ (direct percutaneous endoscopic jejunostomy) insertion at the Department of Gastroenterology and Hepatology in the Catharina Hospital, Eindhoven (the Netherlands), between January 2009 and October 2014 were considered for inclusion in this study (Figure 1). Demographic characteristics were registered in a database. Patients younger than 18 years of age were excluded, as well as those with insufficient follow-up, failed placement, and use of antibiotics before placement.

Figure 1. Flowchart of patients considered for the analysis

PEG procedure

Patients undergoing PEG placement fasted for at least 6h. Oral anticoagulants such as coumarins were stopped for 3–5 days following European guidelines (19). Prothrombin time was measured in advance and indicated as the international normalized ratio (INR). INR should ideally be below 1.5. Platelet aggregation inhibitors such as clopidogrel were stopped for at least 5 days before PEG insertion. No prophylactic antibiotics were administered in advance.

Sedation was performed with intravenous midazolam (mean dose 5 mg), sometimes combined with fentanyl. Pulse oximetry was used for monitoring. All patients also received a single dose of an acetaminophen 1000 mg suppository immediately before the procedure.

In our department, in almost all cases, the ‘pull method’ was used to insert the PEG (Freka PEG; Fresenius Kabi AG, Bad Homburg, Germany). After excluding upper gastrointestinal pathology during a routine gastroscopy, a PEG was placed according to the standard pull technique (as first described by Gauderer et al. (20) and in ESPEN guidelines (1)). The external bolster was attached to the PEG and placement was completed. Antibacterial gauzes were placed around the insertion site and attached with tape. These gauzes were left for 3 days with daily assessment of the insertion site for signs of infection such as erythema, purulent discharge, or irritation and cleaning with dry gauzes and water.

Seven patients underwent the standard ‘push method’ (as first described by Hashiba et al. (14, 21) (Freka Pexact; Fresenius Kabi AG); we included them in the analysis because similar complication rates are found in push and pull methods in the literature (20, 22, 23).

In case of PEG-J tubes: a PEG was inserted as described before, immediately followed by a jejunum extension tube through the PEG tube. The extension was endoscopically pulled to the jejunum (ligament of Treitz) with a grasping forceps.

Endoscopic PEJ was performed according to the PEG pull method, with the only difference being that the infiltration needle was fixed into the small bowel lumen with a loop to prevent migration of the punctured bowel. The trocar was inserted next to and in the same direction as the infiltration needle using this as a guide to the bowel lumen.

After a week, a fistula should have formed. After this first week, the tube was moved daily (carefully pushed 2–3 cm ventrally and pulled back up to resistance) and a daily 360° turn was performed to avoid adhesions and buried bumper syndrome. Feeding was started immediately after placement.

Antibacterial gauzes

The gauzes used in this series were antibacterial drain sponges (Excilon PHMB; Covidien), 10.2×10.2 cm, 6 ply. The gauzes help prevent wound infection because of the presence of the active

ingredient polyhexamethylene biguanide (PHMB), a strong base, in a 0.2% concentration. PHMB has a nonspecific mode of action by interacting with negatively charged acidic phospholipids in the bacterial membrane, eventually leading to increased permeability and death of the bacteria (18). PHMB has a broad-spectrum coverage, including for example *S. aureus*, MRSA, and vancomycin-resistant enterococci.

Data collection

Baseline data collected were sex, age, indication for PEG, comorbidities, use of anticoagulants, and INR (Table 2). Patients using antibiotics before placement (for another indication) were assessed separately as well.

Outpatient follow-up data were collected after 14 days by telephone or outpatient clinic consultation. Inpatient follow-up included daily control of the insertion site until the patient was discharged and a consultation by telephone 14 days after placement.

Patients or their relatives, if patients had problems speaking because of neurological conditions, were asked whether any complication had occurred and whether any complaint or other problem was experienced after PEG placement. In case of complications, patients were asked to visit the hospital for further exploration.

Wound infection was treated with antibiotics on the basis of a clinical assessment. All other complications were documented and treated if necessary (e.g. bleeding).

Retrospectively, all patient files were investigated to determine whether any long-term complications had occurred (with a maximum of 6 years), including mortality.

Table 2. Baseline characteristics of patients

Characteristic	Number (%) [n=331*]	
Sex	199	(60)
Male	132	(40)
Female		
Age (years)	20-102	
Range	68.50	[16,19]
Mean [SD]		
In-/outpatient	179	(54)
Inpatient	152	(46)
Outpatient		
Antiplatelet therapy	39	(12)
Antiplatelet therapy	292	(88)
No antiplatelet therapy		

Characteristic	Number (%) [n=331*]	
INR	328	(99)
< 1.5	3	(1)
> 1.5		
Tube type (%)	283	(86)
PEG	7	(2)
Push-PEG	3	(1)
PEJ	38	(11)
PEG-J		

*n= number of PEG placements in total

Definition of complications

Infectious complications were classified as short term or long term. Infection was classified as erythema (>5 mm in diameter), pain, and purulent discharge, requiring antibiotic treatment (as diagnosed by expert clinical opinion). Minor peristomal erythema or tenderness was not considered infection.

All possible complications after PEG insertion were evaluated, short as well as long term, to compare the overall complication rates with rates found in the literature.

Outcomes/outcome measures

The primary outcomes were minor peristomal wound infections and severe infections such as peritonitis and necrotizing fasciitis. Secondary outcomes were use of antibiotics after PEG insertion, the interval between PEG and onset of infectious complications, and all other complications.

Statistical methods

Data analysis was carried out using SPSS for Windows, version 21 (IBM Corporation, Armonk, New York, USA). Data are presented as frequencies for categorical variables and as mean± standard deviation (SD) for continuous variables. Normal distribution was tested for continuous variables. Continuous albumin and BMI were recoded into categorical values.

Chi²-tests were used to compare categorical data and to estimate odds ratios (OR) and 95% confidence interval (CI) to identify predictors or risk factors of wound infection, early and late complications, and procedure-related mortality. Fisher's exact-tests were used in small sample sizes (if more than one cell or 20% had an expected count less than 5). No multivariate logistic regression was performed as no comparable significant results were found in univariate analysis. All statistical tests were two-sided, with a significance level of 0.05.

Ethical considerations

The present study did not require approval, as confirmed by the Medical Research Ethics Committee of the Catharina Hospital Eindhoven. The Medical Research Involving Human Subjects Act was confirmed not to be applicable to this study. The study was carried out according to the Dutch Codes of Conduct.

Results

A total of 387 PEG procedures were performed, of which 331 were considered for the analysis, in 286 patients. For this study, we focused on the number of PEG placements, not patients.

Indications for PEG are shown in Table 3. The main indications were neurological conditions such as cerebrovascular accidents (24%), Parkinson's disease (17%) and Amyotrophic Lateral Sclerosis (14%), and malnutrition necessitating long-term feeding by a tube (12%).

Table 3. Indications for Percutaneous Endoscopic Gastrostomy (PEG)

Indication	No.(%) n=331
Cerebrovascular accident	79 (24)
Parkinson's disease	55 (17)
Amyotrophic lateral sclerosis (ALS)	47 (14)
Malnutrition; long-term tube feeding	41 (12)
Other neurological/neuromuscular disease (e.g. MS, MSA, paresis, dystrophia, spinal muscular atrophy)	34 (10)
Head and neck malignancy	27 (8)
Dysphagia (not otherwise specified)	26 (8)
Esophageal cancer	11 (3)
Coma/Vegetative condition (traumatic brain injury)	3 (1)
Malignancy not otherwise specified	3 (1)
After radiation therapy	3 (1)
Dementia	2 (1)

Main results

An infection rate of 9.4% within 14 days was found. This includes severe infections such as peritonitis (1.2% of cases) and minor infections (8.2%). All the infections included in the analysis were treated with antibiotics. Of these early infections, 42% developed within 24 h, 29% developed within 1–3 days, 13% developed within 3–7 days, and 16% developed within 7–14 days.

Minor wound infections were found in 27 patients (8.2%), four patients developed a severe infection, all peritonitis (1.2%). Ten cultures of wound infection were collected; two showed only normal skin bacteria. *S. aureus* was found in two patients and *Escherichia coli* was found in two other patients. The other four cultures contained two or three species (consisting of *S. aureus*, *E. coli*, *Candida albicans*, *Enterococcus faecalis*, *Acinetobacter ursingii*, *Morganella* spp., *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Klebsiella pneumonia*, *Klebsiella oxytoca*, and *Hemolytic streptococcus*

group C). No MRSA was found. In all patients who developed peritonitis, cultures were taken, showing *Pseudomonas aeruginosa* (n=1) and *C. albicans* (n=1); two cultures showed no growth.

No significant association was found between sex, in/outpatients, use of anticoagulants or antiplatelet therapy, tube type (PEG, PEG-J and PEJ), INR, and indications compared with wound infection (Table 4). All these variables cannot be defined as risk factors for development of wound infection or other complications.

Table 4. Univariate analysis of wound infection

	No infection (%)	Peristomal infection (minor and major) (%)	p-value
No. of patients (n=331)	300 (90.6)	31 (9.4)	
Sex	185 (55.9)	14 (4.2)	0.074
Male	115 (34.7)	17 (5.1)	
Female			
In-/outpatient	165 (49.8)	14 (4.2)	0.25
Inpatient	135 (40.8)	17 (5.1)	
Outpatient			
Antiplatelet/anticoagulants	267 (80.6)	25 (7.6)	0.235
None	33 (10.0)	6 (1.8)	
Antiplatelet therapy			
Tube type (%)	257 (77.6)	26 (7.9)	0.789
PEG	7 (2.1)	0	1.000
Push-PEG	2 (0.6)	1 (0.3)	0.256
PEJ	34 (10.3)	4 (1.2)	0.768
PEG-J			
INR	297 (89.7)	31 (9.4)	1.000
< 1.5	3 (0.9)	0	
> 1.5			
Comorbidities	261 (78.9)	22 (6.6)	0.028
None	5 (1.5)	1 (0.3)	0.448
COPD	8 (2.4)	3 (0.9)	0.073
Heart failure	22 (6.6)	4 (1.2)	0.109
Diabetes Mellitus	1 (0.3)	0	1.000
Muscle disease	2 (0.6)	0	1.000
Hemodialysis	1 (0.3)	1 (0.3)	0.179
Immunosuppressives			

	No infection (%)	Peristomal infection (minor and major) (%)	p-value
<i>Indications</i>	49 (14.8)	6 (1.8)	0.667
Parkinson's disease	36 (10.8)	5 (1.5)	0.564
Malignancy	72 (21.8)	7 (2.1)	0.860
CVA	4 (1.2)	0	1.000
MS	40 (12.1)	7 (2.1)	0.176
ALS	26 (7.9)	1 (0.3)	0.564
Dysphagia*	3 (0.9)	0	1.000
Post radiation	39 (13)	2 (0.6)	0.398
Malnutrition	25 (7.6)	2 (0.6)	1.000
Neurologic	1 (0.3)	0	1.000
Dementia	2 (0.6)	1 (0.3)	0.256
Coma	3 (1.0)	0	1.000
MSA			

*not caused by any of the listed indications

Multivariate analysis was not carried out as only one univariate risk factor was found. Patients with any comorbidity have a significantly higher risk at developing a peristomal infection [$p=0.028$, OR 2.738 (1.176–6.376)]; however, no single comorbidity was found to have significance in the univariate analysis of all peristomal infections.

In Table 4, the results for univariate analysis are presented. All tests were also performed for minor infection alone, major infection alone, all early complications, and procedure-related mortality; there were no significant results and are therefore not shown.

No side effects or allergic reactions to the gauzes were observed in this study.

Procedure-related mortality

Three patients with already known dysphagia died of aspiration pneumonia (0.9%), which was scored as a PEG-related complication because aspiration pneumonia developed within 2 days after the procedure. No peristomal infection-related mortality was encountered. Overall causes of mortality and interval after PEG were not reproducible in many cases. However, by the end of the study, 42% of patients had died (maximum follow-up 6 years).

Patients using antibiotics before PEG

Patients using antibiotics before PEG insertion were excluded from the analysis. A separate analysis was carried out to estimate the effect of antibiotics, administered intravenously or orally, combined with an antibiotic gauze. Thirty-six patients used antibiotics around (before and after) PEG insertion with another indication for 7–10 days. Twelve patients received prophylactic antibiotics (amoxicillin/clavulanic acid) plus an antibacterial gauze as their immune status was not optimal at the time of

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the PEG procedure. In no patient with previous antibiotic therapy was the guideline-recommended intravenous cefazolin administered. Two out of 50 patients developed a peristomal wound infection (infection rate of 4%).

Discussion

This single-center retrospective study describes the results on the use of antibacterial gauzes in preventing early peristomal infections in a series of 331 PEG (including PEG-Js and PEJs) insertions in 286 patients. An infection rate of 9.4% was found within the first 2 weeks after PEG insertion, which is comparable with the lowest rates reported in the current literature on intravenous antibiotic prophylaxis (9.4–15% infections)(1, 3, 5, 7).

A recent systematic review shows an advantage of intravenous antibiotics compared with no prophylaxis (9.4 vs. 24.2%)(8). In our study, none of the patients received any prophylaxis, but a group (n=50) used a combination of antibiotics and antibacterial gauzes. This group was excluded from the infection rates mentioned above, but interestingly, had a low incidence of 4%.

The results of this study may have implications for current practice. The number of wound infections (minor as well as major) appears to be consistent with the current literature. Normally, antibiotic prophylaxis is administered before the procedure to be effective during the procedure. It is considered that bacteria are mostly transported to the infection site at the time of PEG placement by pulling the tube throughout the oropharyngeal canal. The antibacterial gauzes are placed later, so bacteria may already be present at the tube site. Nevertheless, no difference in infection rates was found on comparing our study with the current literature. Thus, the question arises whether or not the periprocedural protection has a remarkable effect. Our results imply that the use of antibacterial gauzes is safe and effective and can, on the basis of our study, be used as a substitution for single intravenous antibiotic prophylaxis. The results question the need to use intravenous antibiotics in PEG placement. This could be very important regarding the upcoming problem of antibiotic-resistant bacteria and the proper use of antibiotics (24). Antibacterial gauzes have not shown any resistance so far (18). In addition, intravenous antibiotics may cause discomfort for the patient such as abdominal discomfort, diarrhea, redness, and pain at the insertion site, or an allergic reaction. No side effects of the antibacterial gauzes were found in our series.

PHMB is a safe agent at a concentration of 0.2% as in the gauzes.

The Scientific Committee on Consumer Safety (SCCS) states that: 'PHMB is not acutely toxic by the dermal pathway. From reports on patch tests PHMB sensitization in humans can be considered of low frequency (up to 0.5% in dermatitis patients). The SCCS notes that classification as Skin Sens 1B H317 according to CLP criteria is currently proposed (25).

In addition, the effect of a single administration of antibiotics is short. The prolonged effect of an antibacterial gauze is therefore preferred in our department as we found infection rates in the lowest range (compared with the literature).

The costs of the gauzes are low: €0.65 (\$0.73) per piece. Intravenous cefazolin used in current practice costs €2.88 (\$3.59) per dose, not accounting for the system applied for intravenous medication.

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The cost of the gauzes is approximately five times less than cefazolin, although the absolute cost advantage is low.

Currently, no other trials considering the use of antibacterial gauzes have been published. Two studies evaluated the effect of Glycogel® gauzes in preventing complications after PEG insertion; in one study, an infection rate of 12% was found, with Glycogel® as well as standard wound care, and in the other, an infection rate of 14.7% was found with Glycogel® versus 47.05% in standard wound care (4, 26). However, glycerin-containing gauzes are bacteriostatic (glycerin concentration of 65%), whereas the PHMB gauzes that we used are bactericidal. The addition of Betadine® to antibiotic prophylaxis reduced the number of infections (9%) in a small trial, but the use of Betadine® spray alone led to high infection rates (43%)(27).

In patients using antibiotics (for another indication) before PEG in this study, who also received an antibacterial gauze, a peristomal infection rate of 4% was found. The antibiotic use in our study is, however, not completely comparable with previous studies using cefazolin as prophylaxis; the antibiotics administered are variable in type as well as duration of therapy. Although a randomized-controlled trial comparing an antibacterial gauze alone and a combination of the gauze with a single administration of cefazolin is lacking, this retrospective analysis may indicate that the combination of both prophylactic treatments might provide the best prophylaxis.

All complications that might occur after PEG placement were evaluated and compared with the literature. Early complications were observed within 14 days; late complications were evaluated until the end of this study, with a maximum of 6 years of follow-up.

Three patients developed a buried bumper syndrome after more than 6 months (0.9%); two PEG tubes were removed endoscopically and one was repositioned endoscopically. No surgical treatment was necessary.

Bleeding occurred in seven patients (2.1%), none of whom needed endoscopic treatment or transfusion. No bleeding occurred in patients using antiplatelet therapy (acetylsalicylic acid and/or NSAIDs). Procedure-related mortality is reported to be around 1%, caused by aspiration pneumonia or peritonitis in most cases (15, 28). We found a similar procedure-related mortality rate (0.9%) caused by aspiration. This was likely to be related to the PEG procedure, but the indication itself (cerebrovascular accident with recurrent aspiration) could also have been the cause.

All other complication rates were comparable with those in the literature, including peristomal leak (3.3%), dislocation (4.2%), ileus (0.3%), and deterioration of skin (2.4%).

Not all infections were cultured. We found a mixture of species, with *S. aureus* and *E. coli* occurring most frequently. However, the numbers are low; a validated statement or comparison cannot be made. Culture of the infection site is in general not useful (1).

Delayed wound healing might be a risk factor for development of infectious complications after PEG placement (16). This includes patients with diabetes mellitus, immunosuppressive medication, low immune status, or a high leukocyte count. A C-reactive protein greater than 21.5 mg/l was found to increase the risk of mortality (16); a low albumin count (both below 28 g/l (17) as well as below 31.5 g/l (16)) was also found to be a risk factor. Placement of the internal bolster at the upper body of the stomach, high leukocyte count, and an inexperienced endoscopist were also associated with a higher risk of complications in the literature (17). The risk of developing a wound infection in particular is increased in patients with liver cirrhosis, malignancy, and exposure to radiotherapy (26). Development of necrotizing fasciitis is associated with diabetes mellitus, malnutrition, immunosuppression, and patients with wound infection (16). In our study, no relation with comorbidity was found. Albumin levels were not systematically tested.

This study has a few limitations: first, the retrospective nature and the lack of a control group. Second, our group is heterogeneous as all PEG insertions were included independent of the indication for PEG placement. Third, PEG, PEG-J (PEG with extension up to jejunum), and PEJ placements were included. These different types, however, showed no significant difference in infection rates when analyzed individually. Analysis of 283 PEG insertions only showed a 9.1% infection rate: PEG-J, 10.5%. Three patients received a PEJ; one of them developed an infection (33.3%). Interestingly, out of seven Push-PEGs, no patients developed an infection. However, these are very small samples. Overall, the results of our study in a representative group of patients show comparable results as found in current practice. Future research should include a prospective randomized-controlled trial to compare the antibacterial gauzes with intravenous antibiotics or with a combination of both.

Conclusion

The results of this retrospective study support the safe and effective use of antibacterial gauzes in preventing peristomal wound infections after PEG placement. Comparable incidences of infections, minor as well as major, were found, as well as other complications and procedure-related mortality compared with the literature on prophylactic antibiotics. For further validation of these findings, a prospective comparative study should be carried out.

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Percutaneous Endoscopic Gastrostomy under conscious sedation in patients with Amyotrophic Lateral Sclerosis is safe: an observational study

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Abstract

Background

Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disease that causes muscle weakness with respiratory and swallowing dysfunction, eventually leading to death. Permanent enteral feeding is indicated in almost all patients. A percutaneous endoscopic gastrostomy (PEG) tube is considered the first choice, usually performed under conscious sedation (intravenous midazolam). Guidelines are very cautious with respect to sedation in ALS because of the risk for respiratory complications. In our tertiary referral hospital, conscious sedation has been used for many years. Our aim was to review 30-day complications in PEG performed under conscious sedation in ALS patients (without noninvasive positive pressure ventilation (NIPPV) during the procedure).

Patients and methods

A retrospective review, including all ALS patients undergoing PEG under conscious sedation from October 2009 to April 2016, was performed.

Results

Analysis included 45 patients (44% men) receiving intravenous midazolam sedation (mean dose 5 mg) during PEG placement, age 36–91 years (mean: 68.7 years). Forced vital capacity (FVC) was 24–116% (mean 68%), of which mild to moderate dysfunction (FVC 50–69%) was present in 42.2% of patients and (very) severe dysfunction (FVC <50%) in 8.8%. No respiratory complications (e.g. aspiration pneumonia) were observed. Other complications, for example, infection, bleeding and peritonitis occurred in respectively, 8.9, 2.2 and 0%. Mean survival after PEG placement was 13.4 months (range: 1–45 months).

Conclusions

Conscious sedation during PEG insertion in ALS patients did not lead to respiratory complications or to an increase in other complications. Our data indicate that conscious sedation can be used safely in ALS patients with mild to moderate pulmonary dysfunction.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disease that causes muscle weakness with respiratory and/or swallowing dysfunction, cramps, fasciculations and spasticity, eventually leading to death. In the Netherlands, 300–450 patients per year are diagnosed (1). A worldwide incidence of 2–3/100 000/year has been reported (2). The pathophysiology of ALS is still poorly understood. Genetic factors have been identified, with a focus on dysfunction in RNA metabolism and protein homeostasis (2, 3). The gradually progressive course differs among patients. Mostly, muscle weakness and atrophy are the first symptoms, occurring in the arms, legs or the bulbar system (all three in 1/3 of patients), with progression to more central (bulbar) functions, for example, speaking and swallowing. In a very small proportion of patients, dyspnoea is the first symptom, caused by weakness of the respiratory muscles (4, 5).

Generally, four phases are distinguished. At the start, symptoms are mostly mild (stage 1, involvement of one region). Stage 2a is the time of diagnosis. The next phases are characterized by progressive muscle weakness and involvement of the second (stage 2b) and third region (stage 3). In stage 4a, a gastrostomy is needed. The last terminal phase (stage 4b) is characterized by progressive weakness of respiratory muscles, with a need for noninvasive positive pressure ventilation (NIPPV) (4). The median survival at the time of diagnosis is 32 months (6). Swallowing disturbances, muscle atrophy, upregulation of metabolic activity (hypermetabolism) and a change in metabolism (by a lower activity level and elevated ventilation rate because of respiratory insufficiency), together with exhaustion because of eating, lead to weight loss (3). This weight loss further deteriorates quality of life and shortens survival (3, 7, 8). Thus, prevention of weight loss is an important clinical imperative in ALS. As a result, an indication for permanent enteral feeding arises in almost all patients. Currently, a percutaneous endoscopic gastrostomy (PEG) tube is considered the first-choice method for long-term enteral feeding (5, 9, 10). Because of the invasiveness, PEG placement is usually performed under conscious sedation with intravenous midazolam and/or fentanyl. The risks and complications of procedural sedation for PEG placement on ALS patients have not been substantiated.

The Dutch Guideline 'PEG in ALS' states: 'sedation elevates the risk of respiratory complications, for it changes the normal respiratory response in case obstruction or apnoea occurs' and 'the administration of sedatives results in a higher mortality risk' (1), but evidence with respect to PEG procedures is lacking. The European Federation of Neurological Societies guideline states that PEG placement before the occurrence of respiratory insufficiency ($\leq 50\%$) is recommended (5). A low FVC during PEG placement might increase the risk of mortality because of respiratory insufficiency (11, 12). PEG placement is one of the most invasive and high-risk endoscopic procedures and in addition, ALS patients are very vulnerable. A cautious approach is therefore required. Our department has a dedicated team of gastroenterologists, nurses and dieticians to optimize the care around PEG

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insertion and follow-up. Long-term results from our center show a complication rate comparable to that reported in the literature (13). Historically, sedation has always been provided to ALS patients during PEG

placement in our centre. No exceptional PEG-related problems have been observed to date. Our strategy deliberately deviates from that of the Dutch guideline. Therefore, an objective analysis of our data is relevant.

We hypothesize that in our hands, the risk on respiratory complications and procedure-related mortality is not elevated when administering conscious sedation (with midazolam) to ALS patients undergoing PEG placement, even in patients with mild to moderate pulmonary dysfunction (FVC 50–70%).

This study describes the results of PEG insertion under conscious sedation in a single tertiary referral centre. Our primary aim was to analyze complications occurring as a result of sedation. The secondary aims were to analyse other complications related to PEG insertion, use of PEG and mortality (30-day and overall).

Methods

A retrospective review was performed to evaluate complications following PEG placement in all ALS patients who underwent PEG under conscious sedation from October 2009 to April 2016 in the Catharina Hospital Eindhoven, a tertiary referral centre. In case of insufficient follow-up data, use of propofol or no sedation, patients were excluded from the analysis.

Procedure

All patients visited the outpatient clinic before PEG insertion. PEG placement was performed according to the standard pull-method (14). Lidocaine was injected at the insertion site as a local anaesthetic into all the layers of the future PEG tract, including the stomach wall. No antibiotics were administered before the procedure; instead, an antibacterial gauze was placed around the insertion site immediately after the procedure for three days as described in our recent publication (13). Oral anticoagulants were paused (preferable international normalized ratio <1.5 in case of vitamin K antagonists) as well as platelet aggregation inhibitors. COX inhibitors were continued. Sedation was administered to all patients, mostly in a two-step approach (dose titration), with monitoring of blood pressure, heart rate and oxygen saturation by pulse oximetry. No contraindications for referral to an anaesthesiologist were present and service was available in case emergencies or problems occurred. Our department has extended experience with the administration of sedation in endoscopy procedures, also in high-risk procedures. Patients were observed in the day care unit for at least 2h.

Data collection

Baseline data collected from medical records were sex, age, interval between diagnosis and PEG insertion, and between insertion and death, comorbidities and forced vital capacity (FVC). Outpatient follow-up data were collected after fourteen days by telephone or outpatient clinic consultation and annotated in patients' files. Patients or relatives (in case of problems with speaking) were asked whether any complications or adverse events had occurred. All complications were documented and treated if necessary. Retrospectively, all patient files were investigated to determine whether any long-term complications had occurred (with a maximum of 6 years) and survival analysis was carried out.

Outcome measures

The primary outcome was the occurrence of complications, attributable to the procedure (≤ 30 days), respiratory as well as other complications. The secondary outcomes were long-term complications, PEG usage (complete or partial enteral feeding), time between placement and start of use, term of use, 30-day mortality and overall survival after PEG.

Statistical methods

Data analysis was carried out using SPSS for Windows, version 23 (IBM Corporation, Armonk, New York, USA). Data are presented as frequencies for categorical variables and as mean $\pm$ SD for continuous variables. Normal distribution was tested for continuous variables. χ^2 -Tests were used to compare categorical data and t-tests for continuous data. To estimate odds ratios and 95% confidence intervals to identify predictors or risk factors of complications and mortality, χ^2 -tests were used. Fisher's exact tests were used in small sample sizes (if more than one cell or 20% had an expected count <5). No multivariate logistic regression was performed as no comparable significant results were found in the univariate analysis. All statistical tests were two-sided, with a significance level of 0.05.

Ethical considerations

The present study did not require approval, as confirmed by the Medical Research Ethics Committee of the Catharina Hospital Eindhoven. The Medical Research Involving Human Subjects Act was confirmed to not be applicable to this study. The study was carried out in full accordance with the Dutch Codes of Conduct.

Results

A total of 48 ALS patients underwent PEG placement between 2009 and 2016 at our institution. Three patients were excluded from the analyses as they received no sedation (n= 1) or propofol sedation (n=2, clinical preference of one gastroenterologist). A total of 45 patients were included in the analysis. Baseline characteristics are listed in Table 1. The technical success rate of PEG placement was 100%.

Table 1. Baseline Characteristics

	N (total n=45)(%)
Sex	20 (44.4)
<i>Male</i>	25 (55.6)
<i>Female</i>	
Age	36-88y
<i>Range</i>	68.69 [12.1]
<i>Mean [SD]</i>	
Origin	15 (33.3)
<i>Bulbar</i>	11 (24.4)
<i>Limb</i>	11 (24.4)
<i>Mixed</i>	1 (2.2)
<i>Genetic</i>	1 (2.2)
<i>FTD/mixed</i>	6 (13.3)*
<i>Unknown</i>	
Body Mass Index (BMI)	2 (4.5)
≤18	24 (53.3)
20-25	9 (20)
25-30	6 (13.3)
≥30	4 (8.9)
<i>Unknown</i>	
Forced Vital Capacity (FVC)	24-116%
<i>Range</i>	68.4% [18.1]
<i>Mean [SD]</i>	
FVC – values	16 (35.6)
≥70%	13 (28.9)
<i>Mild (60-69%)</i>	6 (13.3)
<i>Moderate (50-59%)</i>	2 (4.4)
<i>Severe (30-49%)</i>	2 (4.4)
<i>Very severe (<30%)</i>	6 (13.3)
<i>Unknown</i>	
Comorbidities	1 (2.2)
Diabetes Mellitus	44 (97.8)
None	

*total 99.8% due to round off

Sedation

Intravenous midazolam was used for conscious sedation. Dose ranges were 2.5–7.5 mg, but 87% received 5mg (2.5 mg: 8.6%; 7.5 mg: 4.4%). Five (11%) patients received fentanyl (mean dose 80µg, range: 50–100µg) combined with standard midazolam. At the very beginning of PEG placement in ALS in our hospital, flumazenil (a midazolam antagonist) was administered as a preventive measure, after completion of the insertion, in three patients. No flumazenil was necessary for hypoxemia or hypoventilation. Short periprocedural hypoxia was found in one patient, with rapid recovery after extra oxygen administration (through a nose sponge).

Forced Vital Capacity (FVC)

FVC ranged between 24 and 116% (mean 68.4%). A mild to moderate impairment was found in 42.2% of patients, and severe to very severe impairment (FVC <50%) in 8.8%. In 13.3%, values were unknown. One of these patients was not able to enclose the mouthpiece. In others, no documentation was found.

Complications

No respiratory complications, such as respiratory insufficiency or (aspiration)pneumonia, occurred within 30 days after PEG placement. All other complications are listed in Tables 2 and 3. One patient had bleeding requiring surgical suturing and four patients developed a peristomal infection requiring antibiotic treatment (8.9%). No peritonitis occurred. One patient developed a small bowel ileus, with rapid recovery after interrupting tube feeding for a few days. Univariate analysis indicated no risk factors for any of the complications that occurred. No significant association was found between sex, FVC, sedation, BMI, age or origin of symptoms compared with any of the early and late complications. Therefore, no multivariate analysis was carried out.

Table 2. Early complications (≤ 30 days)

	N (total n=47*) (%)
Respiratory	
Periprocedural	0
Aspiration pneumonia	0
Local irritation(wound care)	1 (2.2)
Infection (antibiotics)	4 (8.9)
Peritonitis	0
Bleeding (requiring sutures)	1 (2.2)
Peristomal leak	4 (8.9)
Ileus	1 (2.2)
Dislocation	1 (2.2)
Obstruction	1 (2.2)
Pain (minor, spontaneous relief)	6 (13.3)
None	29 (64.4)

**in some patients more than one complication occurred*

Table 3. Late complications (>30 days)

	N (total n=45) (%)
Skin deterioration	3 (6.7)
Buried bumper	1 (2.2)
Prolonged pain	2 (4.4)
Replacement	1 (2.2)
None	38 (84.4)

Mortality

The 30-day mortality was zero. An overall survival rate after PEG placement of 13.4 months (range: 1–45 months) was found. At the end of follow-up (maximum 6 years), 3 (12%) patients were still alive (12, 17.5, 24 months after PEG placement). In two patients, time of death remained unknown because of shifting to another centre for their ALS care and thereby loss to follow-up. BMI, age, sex, FVC at PEG insertion, amount of midazolam used during the procedure and (start of) use of PEG were not found to be risk factors for mortality in univariate analysis. Follow-up was recorded in our hospital records (medical and endoscopy unit records) as well as in the records of the revalidation centre. For our primary outcome, 100% of data were complete. In seven (15.6%) patients, data considering long-

term use of PEG were missing and in two patients data considering survival were missing. Long-term complications were all registered as patients then returned to our hospital.

Use of Percutaneous Endoscopic Gastrostomy

In most cases, feeding through PEG was started immediately (64.4%). Six (13.3%) patients started using the PEG only after several weeks to months and three (6.7%) did not use it at all. In seven patients, no data were available.

Discussion

In this retrospective case series of PEG insertions in ALS patients under conscious sedation, no respiratory complications such as apnoea, hypoxia, (aspiration) pneumonia or laryngospasms were encountered. The frequency of other PEG-related complications was comparable to that in patients with other indications in our own analysis as well as former published data (13, 15).

Conscious sedation is often feared in ALS patients and was even advised against in the Dutch National Guideline (1). The European guideline is very cautious considering sedation as well (5). These advices are, however, based on scarce and very limited data, with low level of evidence (class III–IV) (1, 5). The AAN guideline does not even mention sedation in PEG placement (16). A few other studies have reported on safe sedation with midazolam (and one study with propofol) in patients with a FVC less than 50% undergoing PEG placement. However, to date, in all studies, NIPPV was used during the procedure, contrary to our experiences (17–19). Recently, Dorst et al. (20) reported that PEG could be performed safely even in advanced stages of ALS. In their study, 20 patients received general anesthesia during PEG placement; in 65 patients, only local anesthetics were administered. The effect of conscious sedation was not studied (20). In our study, sedation was used safely, even in patients with mild to moderate respiratory dysfunction. On the basis of these results, we postulate that safe use of conscious sedation during PEG placement in ALS patients is possible and deserves broader evaluation and application in care for ALS patients.

The timing of PEG in ALS patients remains a difficult decision that should be made on the basis of several criteria. Most importantly, PEG feeding should prevent (further) weight loss as this is a well-known poor prognostic factor (7,16). Second, safe insertion is a key point in this very frail patient group. Third, patient comfort during PEG insertion should be ensured. Currently, no evidence-based advice on the timing of PEG can be given because of insufficient data (5, 16). Guidelines recommend placement before FVC falls below 50% to decrease the risk (1, 5, 16). Evidence is of low level (III–IV) on the basis of few small sample size retrospective studies (10, 21–23). The increasing risk of aspiration pneumonia with progression of the disease is seen as a strong argument in favor of PEG placement (1). Gastrostomy feeding is believed to reduce the risk of aspiration; however, no convincing evidence to support this belief has been found yet (5, 10, 24).

In contrast, fear of respiratory complications because of low or declining FVC might result in too early placement, without ever using the PEG. Our results do indicate a low risk for respiratory complications in patients that have been referred in time for PEG placement. Regular evaluation of lung function was part of the follow-up. The counterpart of this careful approach with measuring lung function regularly, and thereby early placement of PEG, is the fact that six (13.3%) patients started using PEG only after a few months and three (6.7%) patients did not use the PEG at all. Preventive PEG

placement is confronting for patients and points towards progression of their disease. It is therefore often experienced as very unpleasant as it points towards progression of their disease. Despite our advices on the risks, patients prefer placement in a later phase of their disease (25).

Although a low or a rapidly declining FVC in ALS patients often determines the timing of PEG insertion, use of FVC as the most important variable is questionable. FVC has proven to be a poor predictor of respiratory failure (26) and of diaphragmatic weakness (27). Recently, Dorst et al. (20) reported that FVC does not influence the periprocedural survival of patients after PEG. This is in line with the findings obtained by and Kak et al. (28) Sarfaty et al. (29).

Measurement of lung function through FVC is difficult to perform in ALS patients with bulbar involvement because of trouble with enclosing the mouthpiece. In addition, patients often do not have enough strength to perform a forced expiration. Therefore, forced expiration may not be a representative predictor for the safety of the intervention under conscious sedation. Diffusion capacity, measured by CO₂ in expired air, preferably overnight, may prove to be more accurate. In the Netherlands, this procedure is currently only used as a measurement in overnight home ventilation and has not been evaluated as a predictor for the safety of PEG placement.

In general, sedation may result in respiratory side effects, such as hypoxia, hypercapnia, aspiration and related pneumonia. Midazolam might cause pharyngeal dysfunction and a disturbance of breathing coordination. There is a risk of apnoea and hypoventilation of up to 15.4%; however, severe events are very rare. The reported overall frequency of respiratory arrest is 0.099% (30, 31). In our series, with midazolam sedation, no pulmonary complications occurred. Recently, conscious sedation with propofol, administered in the endoscopy room by trained personnel, has become more common for invasive endoscopic procedures including PEG. Because of its short time of action and more accurate titration of dose, propofol seems to be a suitable alternative for midazolam sedation. However, a higher risk for assisted ventilation was found in interventional endoscopy procedures when using propofol (32). In ALS, safe PEG placement with propofol sedation was shown in patients with FVC less than 50%, but with the use of bi-level positive airway pressure ventilation during placement (18).

Possible enteral feeding alternatives for PEG in ALS patients are PRG and surgical gastrostomy or jejunostomy. PRG and PEG are comparable considering the complications and mortality (9,33). PRG was found to have a higher success rate (100%) compared with PEG (85.6%) in ALS patients (34). Our data point to a 100% success rate for PEG. In general, no sedation is necessary in PRG. It has a comparable procedure-related and 30-day mortality in ALS (11, 33, 35, 36). However, PRG is not readily available in all centers and is known to have a higher rate of dislocation (40 vs. 6% in PEG) (37). Surgical gastrostomy and jejunostomy are associated with higher morbidity, up to 29% (38–40), and

are therefore (1% of cases) performed very rarely in ALS (33). Total parenteral nutrition should only be used as a last resort in patients with severe respiratory insufficiency (41–43).

Survival

The 30-day survival rate in our group was 100%. The largest prospective trial to date reported a 30-day mortality of 4% (33), but rates of 25% (44) have also been reported. Mathus-Vliegen (45) as well as Kasarskis et al. (22) reported a higher risk of 30-day mortality in patients with an FVC less than 50% (9.6 and 11.5%, respectively). In our group, only four ALS patients had a FVC less than 50%. Mortality at 30 days was zero. Overall mortality during the entire study interval was 88%, not related to PEG placement or to the use of sedatives. The mean survival after PEG placement was 13.4 months (range: 1–45 months). These data are comparable to previous literature data (varying from 5 to 19 months) (11, 12, 20, 44, 46). The overall survival of an ALS patient starting from diagnosis is 32 months (6). The major strength of the current study is that it is the first to address safe conscious sedation in ALS patients without using NIPPV during the procedure. Furthermore, our analysis included 45 patients with negligible loss to follow-up, and uniform preinterventional, peri-interventional and postinterventional care. Our data add new information to that from previously published studies on PEG placement and conscious sedation in ALS (17–19).

Limitations

The limitations of this study relate to its retrospective nature and the lack of a control group. There are missing data for two secondary outcomes (overall mortality and use of PEG for enteral nutrition), and therefore, a risk of bias is present. Our series included a relatively large group of patients with moderately impaired pulmonary function compared with previous reports with patients with more severe impaired pulmonary function. Nevertheless, other risks of bias are low as all patients referred for PEG were included in the analysis.

We postulate that in a setting with an experienced and dedicated team, conscious sedation is safe and a considerable option during PEG insertion. Our results, hopefully, will open the discussion on this subject in favor of patient comfort, without impairing safety. Because of the retrospective nature of the study and the lack of a control group, our results should ideally be confirmed in randomized-controlled trials. Future research should also focus on the exact influence of varying sedatives on respiratory muscle in ALS. In addition, comparison of CO₂ diffusion with FVC as a measurement of lung function in ALS could be of interest to determine timing and safe PEG insertion more accurately.

Conclusion

We have shown that in experienced hands, the risk of respiratory complications and procedure-related mortality with conscious sedation (with midazolam) in ALS patients undergoing PEG placement is absent, even in patients with mild to moderate pulmonary dysfunction. Confirmation of our results by data from other centers is needed. Here, we contribute towards a discussion on the safety of sedation in a high-risk endoscopic procedure in a group of very frail patients. Although more extensive data are needed, our findings are in favor of revision of guidelines on PEG placement in ALS patients.

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D

ALTERNATIVE APPLICATIONS OF PEG

Therapeutic strategies in gastroparesis:
results of stepwise approach with diet and
prokinetics, Gastric Rest and PEG-J

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6

Abstract

Background

Gastroparesis is characterized by abnormal gastric motor function with delayed gastric emptying in the absence of mechanical obstruction. In our tertiary referral center, patients are treated with a stepwise approach, starting with dietary and lifestyle advice and prokinetics. When these initial measures/interventions fail, in the presence of malnutrition, three months of nasoduodenal tube feeding with 'gastric rest' is prescribed. When not successful, placement of a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) for long term enteral feeding.

Aim: To evaluate the effect of this stepwise therapeutic approach on weight and symptoms in patients with gastroparesis.

Patients and methods

Analyses of data of all referred gastroparesis patients between 2008 and 2016.

Results

A total of 86 gastroparesis patients (71% female, 20-87yrs (mean 55.8yrs) were analyzed of whom 50 (58%) had adequate symptom responses to dietary measures and prokinetics. The remaining 36 patients (decompensated gastroparesis) were treated with three months of gastric rest with nasoduodenal tube feeding. Symptom response rate was 47% (17/36). Significant weight gain was seen in all patients, independent of symptom response. In the remaining 19 symptom non-responders the enteral feeding was continued through PEG-J. Treatment was effective in 37% with respect to symptoms, with significant weight gain in all. In 84% of patients the PEG-J is still in use (mean duration 962 days).

Conclusion

Following a stepwise treatment approach in gastroparesis, adequate symptom response was reached in 86% of all patients. Weight gain was achieved in all patients, independent of symptom response. Diet and prokinetics were effective with regard to symptoms in 58%, temporary gastric rest in 47% and PEG-J as third step in 37% of patients.

Introduction

Gastroparesis is a chronic disorder of the stomach characterized by delayed gastric emptying, in the absence of mechanical obstruction. Symptoms of gastroparesis include nausea, satiation, postprandial fullness, vomiting, upper abdominal pain and bloating (1-3). The estimated age-adjusted incidence of gastroparesis in 2007 was 37.8 per 100,000 persons in women, and 9.6 per 100,000 in men (4). The burden of this disorder on individuals (morbidity, quality of life and mortality) and society (health care costs and indirect costs through productivity loss) is considerable (4, 5).

Although gastroparesis is frequently associated with diabetes (diabetic gastroparesis, DGP), idiopathic gastroparesis (IGP) accounts for the majority of cases (60%). Other known causes of gastroparesis are surgery (e.g. bariatric, anti-reflux), related to vagotomy, medications, metabolic derangements or following bacterial or viral infections (6, 7). The pathophysiology of gastroparesis is incompletely understood. Several mechanisms have been postulated including impaired gastric accommodation, antral hypomotility, dysregulation of antroduodenal coordination (8), pyloric dysfunction and excessive inhibitory duodenogastric feedback (9-11).

Gastroparesis can be classified based on the severity symptoms into the following categories: grade 1 gastroparesis with easily controlled symptoms and the ability to maintain weight and nutrition status on regular diet or with minor diet changes; grade 2 is compensated gastroparesis, in which symptoms are moderate, with partial control by medication, ability to maintain nutritional status with dietary and lifestyle adjustments, and occasional hospital admissions. Grade 3 is decompensated gastroparesis and occurs when symptoms are refractory despite medical therapy. In decompensated gastroparesis, nutritional status cannot be maintained via oral intake and hospital admissions or emergency room visits are frequent (2, 12).

Due to an incomplete understanding of gastroparesis and limited therapeutic options, symptom management is challenging. Nutritional interventions are often necessary. Initial treatment generally consists of dietary interventions (e.g. intake of small and frequent meals) and restoring glycemic control in diabetic patients (13, 14). Dietary advices are often combined with use of prokinetic agents such as dopaminergic-2-antagonists (e.g. domperidone, metoclopramide), motilin-analogues (e.g. erythromycin) or serotonin₄ (5-HT₄)-agonists (e.g. prucalopride). However, lack of robust evidence for their effectiveness in addition to potential serious side effects (QT-prolongation) or tachyphylaxis limit the chances for a therapeutic benefit (15-17). With regard to nutritional support, consensus has been reached that nasoduodenal tube feeding should be considered in case patients have significant

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weight loss (5-10% in respectively 3-6 months), are unable to achieve their target weight, or when repeated hospital admissions for malnutrition or dehydration are necessary (3, 18, 19).

In our tertiary referral center (Maastricht University Medical Centre, Maastricht UMC+), we provide medical and nutritional support according to a stepwise approach, starting with dietary and lifestyle advice and prokinetics. When these initial measures fail, in the presence of malnutrition (grade 3 gastroparesis), three months nasoduodenal tube feeding with the aim to achieve 'gastric rest' (GR) and 'gastric decompression' is considered. Thereafter oral feeding is reintroduced, in a stepwise fashion and nasoduodenal feeding is stopped. When oral reintroduction fails, placement of a Percutaneous Endoscopic Gastrostomy with Jejunal extension (PEG-J) for long term enteral nutrition is offered.

Aim of the present study was to evaluate the efficacy of our stepwise approach with different interventions (diet and medication; nasoduodenal tube feeding with gastric rest; PEG-J) on gastroparesis symptoms and objective parameters (bodyweight/BMI).

Methods

Records of all referred gastroparesis patients seen between 2008 and 2016 in the Maastricht University Medical Centre (Maastricht UMC+), a tertiary referral center, were reviewed. Patients were identified by reviewing gastric scintigraphy test databases (n=737) and all PEG-J placement (n=496) and DRG codes for gastroparesis (n=99). Patients with documented evidence for delayed gastric emptying of solids by scintigraphy, exclusion of mechanic obstruction by gastroscopy, and symptoms of gastroparesis (defined as nausea, early satiety, postprandial fullness, vomiting, upper abdominal pain and bloating) were included in the retrospective analysis. Medical history was reviewed to assess response to treatment according to our stepwise approach. Data assessment included results of gastric emptying tests and antroduodenal manometry. The local ethical committee gave approval to contact patients for additional information. In case of insufficient data, e.g. in case of loss to follow up, patients were excluded.

Diagnostics

Scintigraphy

In the Maastricht University Medical Center (MUMC) scintigraphy was performed according to standard procedures (20, 21). Medication affecting gastrointestinal tract motility was stopped at least 3 days prior to the study. All participants underwent scintigraphy after an overnight fast.

A standard meal was given to the patient, consisting of 100ml egg whites mixed with 99mTc nanocolloid (microwaved for 2 min), 1 slice of bread with 15g jam, and 120ml radiolabeled (111In DTPA) water. Patients were instructed to finish this meal within 10 min. Immediately after meal ingestion, images were obtained (t=0) as well as 60, 120, and 240 min after the meal.

Six patients were diagnosed with gastroparesis by a short scintigraphy test (90-120 minutes) and one patient was diagnosed by a ¹³C-octanoic acid breath test. As comparison of different tests and/or study protocols is not possible, we only report quantitative results of the recommended four-hour solid phase gastric emptying scintigraphy.

For the four-hour solid phase gastric emptying scintigraphy, total gastric counts were normalized to 100% for t=0 (0 minutes; image directly after meal ingestion). The percentage of contents remaining in the stomach was reported after 60, 120 and 240 minutes. Normal values were 53-79% for 60 minutes, 16-37% for 120 minutes, and 0-4% for 240 minutes, as in the validated standard protocol used at our hospital. Normal values for solid and liquid gastric half emptying time were 64-103 minutes and <22 minutes, respectively.

High resolution antroduodenal manometry

Subjects underwent antroduodenal manometry (ADM) after an overnight fast of at least 8 hours following standard procedures (22-25). Medication affecting gastrointestinal tract motility was

stopped 3 days prior to the study. A solid-state high-resolution catheter consisting of 36 transducers was used (Unisensor AG, Attikon, Switzerland). Transducers were spaced at 1-cm intervals. After 30 min recording in fasting conditions, subjects were given a standardized meal consisting of one scrambled egg, two slices of white bread with 5 mg of margarine and 150 ml of water (283 kcal, 41.2 % fat, 17.1 % carbohydrates, 41.6% protein). After ingestion of the meal, data were recorded for 6 hours, during which patients were not allowed to eat or drink.

During the postprandial period, we determined frequency of valid contractions (contractions per min), contraction amplitude (mmHg) and motility index of antral pressure waves (mmHg). Motility index (MI) was calculated using the formula: $MI = \ln ([\text{number of waves} \times \Sigma \text{amplitude}] + 1)$ in the two pressure sensors located proximally to the manometrically and fluoroscopically defined pylorus, as previously described. Antral hypomotility was considered as a postprandial antral motility index <13.67 mmHg (26).

Treatments

Diet and prokinetic treatment (DP)

Dietary advice consisted of a low-fat, low fiber diet, with frequent small meals, prescribed by a dedicated nutritionist. Prokinetics (erythromycin, metoclopramide, or domperidone) were prescribed in case dietary advice was insufficient.

Our first choice for chronic medication is erythromycin (250 mg tid), for this is most effective in improving gastric emptying and improvement of symptom scores (27). The major issue with erythromycin is tachyphylaxis due to down regulation of the motilin receptor (17) in addition to growing concerns surrounding bacterial resistance and the need for appropriate antibiotic stewardship. Therefore, we rotated treatment cycles, with a maximum period of 4 consecutive weeks of medication with one week "rest". Erythromycin was combined with nutritional support from a dietician. In case patients did not respond to erythromycin, we prescribed domperidone or metoclopramide for 4 week periods. The main issue with these dopaminergic-2-antagonists are its side effects: metoclopramide may evoke tardive dyskinesia, QT-prolongation and depression, whereas domperidone can cause QT-prolongation (2, 28).

Prucalopride was not subscribed as this drug is not reimbursed in the Netherlands.

Gastric Rest (GR)

A nasoduodenal tube was placed endoscopically. Thereafter complete nasoduodenal tube feeding was given for three months (Gastric Rest), with nil per mouth.

PEG-J

A PEG was placed according to the standard pull-method by Gauderer et al (29), with immediate placement of a jejunal extension tube through the PEG tube, which was placed in the proximal jejunum and fixed with an hemoclip (30, 31).

Outcome parameters

Of primary interest was the effect of the interventions (diet and prokinetics; intraduodenal tube feeding with gastric rest; PEG-J) on subjective treatment response, determined according to the Global Physician Assessment Scale (32, 33)(GPA 1: complete relief; GPA 2: marked relief; GPA 3: moderate relief; GPA 4: slight relief; GPA 5: no relief; GPA 6: worsening symptoms), based on the clinical effect reported by the patient during visits to the outpatient department. GPA score was documented four weeks after onset of treatment. Reported complete and marked relief (GPA 1-2) was considered as a successful treatment response (responders). In case treatment was considered not successful (based on repeated symptom scores), patients were classified as non-responders and were offered the next step of treatment. Preferably, each medication was tested for at least a four weeks period. Gastric rest with nasoduodenal feeding was given for 3 months. PEG-J treatment was evaluated regularly, with objective outcomes measured after six months.

Other parameters assessed included the effect on body weight (BMI). In this respect, interruption of weight loss or an increase in weight were considered as treatment success, whereas persistent weight loss was considered as treatment failure.

Success rates of the treatments, occurrence of complications and of side effects were monitored.

Statistical methods

Data analysis was performed using SPSS for Windows, version 23 (IBM Corporation). Normal distribution was tested for continuous variables. Non-parametric tests were used in case of absence of normal distribution. Data are presented as frequencies for categorical variables, and as median (interquartile range; IQR) in case of skewed distributions, or as mean (SD) in case of normal distributions for continuous variables. The Chi²-test or Fisher's exact test (in case of small samples) was used to assess differences between categorical variables, whereas the Mann Whitney U test and Kruskal Wallis test were used for continuous variables. All statistical tests were two-sided, with a significance level of 0.05.

Results

A total of 86 patients diagnosed with gastroparesis (71% female, age range 20-87yrs (mean 55.8yrs) were seen between 2008 and 2016 and their data were analyzed. Idiopathic gastroparesis was the most common type of gastroparesis (n =33, 38.3%), followed by diabetic gastroparesis (n=23, 26.7%), post-surgical gastroparesis (n=23, 26.7%) and generalized motility disorder (including patients with Ehlers Danlos syndrome, n=7, 8.1%). Baseline characteristics, etiologies per treatment group and results of scintigraphy are shown in Table 1.

Groups were defined as follows: Group I consists of patients that only needed DP (responders to DP, 50 patients). Group II consists of non-responders to DP (decompensated gastroparesis), who received GR (36 patients). Group III consists of responders to DP+GR (17 patients), and Group IV of patients that did not respond to DP and GR and therefore received PEG-J (19 patients).

Before treatment (six to twelve months), 31 patients had a stable weight (36%), 27 patients (31.4%) had <10kg weight loss and 28 patients (32.6%) had ≥10kg weight loss. No relation was observed between treatment (symptom as well as weight) response and gastric emptying parameters (data not shown).

Table 1. Baseline characteristics of patients with gastroparesis

Patients with gastroparesis	Total n=86 Median (IQR)	Group I (n=50) DP only	Group II (n=36) DP+GR	p-value Group I vs. Group II	Group III (n=17) DP+GR respond- ers	Group IV (n=19) DP+GR non-re- spond- ers (PEG-J)	p-val- ue Group III vs. Group IV
Demographic parameters							
Age	60.0 (42.8- 67.0)	62.5 (49.5- 69.5)	54.00 (37.3-62.0)	0.008	43.0 (31.0- 62.0)	56.0 (38.0- 62.0)	0.428
Gender (female, %)	71%	70%	72.2%	0.824	70.6%	73.7%	0.838
Etiology	N (%)	N (%)	N (%)	0.491	N (%)	N (%)	0.853
Idiopathic	33 (38.3)	16 (32)	17 (47.2)		7 (41.2)	10 (52.6)	
Diabetic	23 (26.7)	17 (34)	6 (16.7)		4 (23.5)	2 (10.5)	
Post-surgical	23 (26.7)	15 (30)	8 (22.2)		4 (23.5)	4 (21.1)	
Generalized GI motility disorder	7 (8.1)	2 (4)	5 (13.9)		2 (11.8)	3 (15.7)	
Gastric emptying parameters							
T50 solid (min; normal 64-103 minutes)	134.0 (110.0- 177.0)	129.0 (108.5- 180.5)	139.0 (122.8- 174.8)	0.410	145.0 (129.0- 170.0)	129.0 (103.0- 195.0)	0.337
Stasis 60 min (%; normal 53-79%)	83.5 (72.0- 90.0)	81.5 (69.3- 87.8)	87.0 (77.3- 90.8)	0.109	86.0 (76.0-87.5)	90.0 (82.0-93.0)	0.087
Stasis 120 min (%; normal 16-37%)	54.5 (45.0- 73.0)	52.0 (45.0- 72.5)	59.5 (51.0- 73.0)	0.389	59.0 (51.0- 69.0)	61.0(37.0- 73.0)	0.876
Stasis 240 min (%; normal 0-4%)	10.5 (1.0- 27.3)	10.0 (9.0- 28.0)	13.0 (5.0- 27.0)	0.407	14.5 (6.5- 27.3)	11.0 (1.0- 27.0)	0.553

DP = diet and prokinetics, GR= Gastric Rest, PEG-J=Percutaneous Endoscopic Gastrostomy with jejunal extension

Treatment results

Diet and Prokinetics (DP)

All 86 patients were treated with diet and prokinetics.

Outcomes of DP

Of the 86 patients, 50 patients (58%, group I) were symptom responders and did not require further therapeutic interventions (Figure 1). Symptom responders showed no significant change in weight (0.3%, $p=0.719$), whereas non-responders lost a significant amount of weight (6.2kg, 8.7%, $p=0.006$; Table 2) during the treatment phase. The weight change after treatment between symptom responders and non-responders was significantly different ($p=0.005$). Non-responders to DP were significantly younger than responders ($p=0.008$). The differences in scintigraphic parameters were non-significant.

Complications of DP

No complications occurred.

Gastric Rest (GR)

A total of 36 patients (non-responders to DP) were treated with three months of gastric rest by nasoduodenal tube feeding after insufficient response with DP. Enteral tube feeding was well tolerated by all patients.

Outcomes of GR

A total of 17 patients (47%, group III) responded well to GR: these patients were able to discontinue enteral feeding after three months and successfully re-introduced oral intake. Oral intake was combined with medication such as prokinetics (erythromycin, domperidone, metoclopramide) in 65% of patients. Objective weight gain in GR symptom responders was 2.5kg ($p=0.018$ compared to pre-treatment, Table 2).

The other 19 patients (53%, group IV) were non-responders with respect to not being able to discontinue enteral feeding and completely resume oral feeding. These 19 patients also had a weight gain of on average 2.1kg ($p=0.027$) after 3 months of GR. Weight change and weight before and after treatment were not statistically different amongst responders and non-responders to GR (resp. $p=0.433$ and $p=0.531$).

Complications of GR

In the 3 months of GR, complications included occlusion of the nasoduodenal tube in 3 patients (8%) and nasopharyngeal irritation in 2 patients (5.5%), resulting in tube replacement.

Figure 1. Treatment algorithm

Percutaneous Endoscopic Gastrostomy with jejunal extension (PEG-J)

The 19 patients (22% of the total of 86 patients, group IV) with insufficient symptomatic response after 3 months GR continued treatment with enteral feeding through PEG-J. PEG-J placement was successful in all patients. An initial weight loss of mean 3 kg (range 0-13kg, $p=0.002$) was observed after GR was stopped.

In all these refractory patients, antroduodenal manometry was performed to evaluate the presence of a generalized motility disorder in the fed and fasting state prior to PEG-J placement.

Outcomes of PEG-J

Subjective outcome

Marked relief was reported by 36.8% (GPA 2), moderate relief by 36.8% (GPA 3), slight relief in 10.5% (GPA 4). 15.8% of patients reported minor or no relief (GPA 5).

Objective outcome

A significant weight gain of (mean) 5.1kg (range -5 to +21kg, $p=0.002$) was observed within 6 months after PEG-J placement. Symptom responders showed a more pronounced weight gain compared to non-responders (Table 2), although weight and weight change were not statistically different amongst responders and non-responders for PEG-J (resp. $p=0.150$ and $p=0.454$).

Intake

Of all patients receiving enteral nutrition, 16 (84%) were able to have some oral intake in addition to enteral tube feeding, while three patients could not eat or drink anything (16%).

Manometric data (subjective responders vs. non-responders)

Data were eligible for analysis in 17 of the 19 patients (no measurement performed in 2 patients). No significant differences were observed in manometry data (antral amplitude, antral motility index, presence of phase III contractions) between responders ($n=7$) and non responders ($n=12$) to PEG-J, albeit this might be due to a type II statistical error.

Complications of PEG-J

Most frequent complication was luxation of the jejunal extension to the stomach (32% of patients, 1-8 times), occurring after a few months of use, which required placement of a new extension including fixation to the duodenum/jejunum. Other complications were peristomal infection (11% within 30 days, 16% after 30 days, easily treated with oral antibiotics) and buried bumper (3 patients, 16%, after approximately one year which lead to replacement).

Long term outcomes of PEG-J

Only 3 patients (16%) of the 19 patients treated with PEG-J were able to resume complete oral intake. The PEG-J was removed after a mean of 11 months. In 84% of patients (n=16) the PEG-J is still in use, with a mean treatment time of 32 months. Besides PEG-J feeding, 13/19 (68%) of patients needed additional treatment with prokinetics/antiemetic medication. No significant differences were seen in manometric or scintigraphic results of the patients that have been able to completely resume oral feeding compared to patients that still use PEG-J.

Table 2 Objective treatment outcomes in relation to subjective response

	N (total n = 86)	Mean weight (kg) before (SD)	Mean weight (kg) after (SD)	Mean weight change (kg) (%)	p-value (pre vs. post treat- ment)
Diet & prokinetics (n=86)	↓				
Symptom Responders	50	72.3 (14.8)	72.5 (14.9)	+0.2kg (+0.3%)	0.719
Non-Responders	36	73.5 (15.4)	68.4 (13.1)	-6.1kg (-8.3%)	0.006
Gastric Rest (n=36)	↓				
3 months					
Symptom Responders	17	69.5 (13.5)	72.1 (14.7)	2.5kg (3.6%)	0.018
Non-responders	19	65.6 (13.2)	67.8 (15.23)	2.1kg (3.3%)	0.027
PEG-J (n=19)	↓				
6 months					
All	19	64.9 (14.6)	69.9 (16.0)	5.1kg (7.9%)	0.002
Responders 1-2	7*	62.3 (10.7)	70.3(13.6)	8.1 kg(12.9%)	0.026
Non-responders (GPA 3-6)	11*	64.7 (16.4)	68.1 (17.8)	3.5kg (5.4%)	<0.001

*outcomes were missing for 1 patient

Discussion

This study describes the follow-up of a cohort of tertiary referral gastroparesis patients treated with a stepwise approach of standardized interventions. Considering symptom response, diet and prokinetic treatment was effective in relieving symptoms in 58% of patients. In patients refractory to diet and prokinetic treatment, gastric rest with enteral nutrition effectively improved symptoms in an additional 20% (17/86) of patients. In severely decompensated gastroparesis patients who failed to the two previous treatment steps, PEG-J was an efficacious treatment entity in an additional 8% (7/86) of patients. Taken together, our approach resulted in 86% efficacy when combining the results of the three stepwise interventions. In 12 of the 86 patients (14%) we did not achieve an adequate symptom response: 7 patients only had a moderate symptom response and 5 patients had little or no response at all. Another important finding from our study is that the nutritional interventions (applied according to our stepwise approach), resulted in significant weight gain, independent of symptom response.

The overall response to diet and medication (step 1) was 58%, the response to gastric rest with enteral nutrition (step 2) was 47% and the response to PEG-J (step 3) was 37%. The question arises why some patients respond or not respond to the subsequent steps of treatment and which factors contribute to treatment success or failure.

For the first step, medication and diet, we systematically evaluated whether the available prokinetics (erythromycin, domperidone, metoclopramide) had been tried for a period of at least four weeks per medication. The non-responders to diet and prokinetics were characterized by a significantly younger age. Previously, higher age (50 years and older) showed to have better symptom response in one study (34). Scintigraphic parameters were not significantly different between responders and non-responders.

For the second step with gastric rest and enteral tube feeding, no significant differences were observed between responders and non-responders, neither in clinical parameters, nor in cause of gastroparesis, nor in results of scintigraphy.

For the third step with PEG-J, neither clinical parameters, nor results of scintigraphy, nor antroduodenal manometry data were significantly different between responders and non-responders to PEG-J intervention, albeit that this was a fairly small group in numbers. Thus, the response to treatment either in terms of weight or symptoms was not correlated to data of scintigraphy or motility. It therefore appears that gastric motor function characteristics do not affect the response to treatment. This observation is largely in line with the consistent observation that gastric emptying studies (scintigraphy as well as wireless motility capsule) show poor correlation to symptoms of gastroparesis (35-40).

A potential factor that we did not systematically take into account is the presence of psychiatric comorbidities, especially depression or anxiety disorder and whether patients underwent any specific treatment for these conditions that could have influenced treatment response to nutritional interventions. Literature data indicate that psychiatric comorbidities are frequent in patients with gastroparesis: combined anxiety/ depression in 24%, severe anxiety in 12%, depression in 23%, and somatization in 50% (41). Acute anxiety and stress are known for their profound influences on gastric motor function, in particular on gastric accommodation (42). In addition, psychoactive medication has been suggested to influence gastric motility (43) although literature findings are inconsistent (44). This appears relevant as these drugs are often prescribed for relief of abdominal symptoms in patients with gastroparesis even in the absence of apparent psychopathology. It is noteworthy that the NORIG study has recently shown that nortriptyline is not effective for symptom relief in gastroparesis patients (45). Here we argue in favor of routine assessment of psychiatric comorbidities in patients with severe gastroparesis and taking into account psychiatric comorbidities when evaluating therapeutic efficacy of treatment modalities.

Based on literature data, approximately 30% of gastroparesis patients progress to grade III (decompensated) gastroparesis, of which the majority are eventually in need of long term enteral tube feeding (46, 47). In our hands only 19 of 86 patients (22%) progressed to grade III. We have chosen for placement of PEG-J with fixation in the distal duodenum or proximal jejunum. Alternative procedures include jejunostomies either placed via surgery or radiology or endoscopy (48). The surgical approach is known for higher complication rates (49, 50) and experience with (direct) PEJ (Percutaneous Endoscopic Jejunostomy) and Percutaneous Radiologic Jejunostomy (PRJ) in gastroparesis is limited (51-53). In a study assessing the effect of surgical jejunostomy in diabetic gastroparesis, symptom relief was seen in 39%, and improved nutritional status in 56% (48). No data on the efficacy of nasojejunal feeding or the effect of dietary treatment on weight in gastroparesis patients were published earlier. Our choice in favor of the PEG-J procedure with duodenal extension and fixation is based on local expertise of our PEG team and outpatient PEG support.

A procedural success rate of 100% was found in our study for both gastroduodenal tube placement and PEG-J, which is comparable to literature rates (30, 52, 53). In three months of nasoduodenal feeding (GR), occlusion of the tube and nasal irritation occurred at relatively low rates (resp. 8% and 5.5%).

Dislocation is the major disadvantage of PEG-J and occurred in 32% of patients. These rates are in line with literature data, ranging from 25.2 to 55.9% (30, 54). No occlusion occurred, which is described in 3.5-35% of patients with PEG-J (30, 31).

Some limitations of our study should be mentioned. First, it is a retrospective analysis of prospectively collected data. Over the eight years period we did not systematically collect all patient reported outcome measures or systematically characterized psychological factors and psychiatric comorbidities. Second, we serve as tertiary referral centre. Therefore, a small percentage (9%) of the scintigraphic data were collected in other centers with different protocols and normal values and were therefore not eligible for comparison. Thirdly the number of patients we included over 8 years is substantial but limited with respect to subgroup analyses.

A strength of our study is that it is the first study reporting on the stepwise therapeutic approach of gastroparesis and on the role of gastric rest and of PEG-J, with respect to objective as well as subjective treatment outcomes. Moreover, it is the largest study since Fontana in 1996 (including 26 patients receiving surgical jejunostomy), reporting on the effects of enteral tube feeding in gastroparesis (17, 48). Other available studies considering enteral feeding in gastroparesis (surgical or direct jejunostomy) included small populations of two, four and twelve patients (51-53). Our analysis revealed only minor complications using PEG-J (with replacement of the tube in 16% of patients), whereas with the surgical approach, 14/26 patients had one or more major complications (requiring hospitalization or surgery)(48). With direct PEJ the rate of complications was 18.2% (2/11), including volvulus and a jejunocolic fistula (51). Direct PEJ showed lower technical success (78.6%), whereas we had a 100% technical success rate. Only 56% of patients with surgical jejunostomy had improved nutritional status (48), whereas virtually all our patients showed significant weight gain with PEG-J.

Our findings have implications for therapy in patients with severe gastroparesis. First, 86% of the referred gastroparesis patients showed adequate clinical responses to our stepwise systematic approach. Secondly, nutritional interventions aiming to restore the nutritional status are crucial. We persisted in a full three months regime with gastric rest. Gastric rest may lead to decompression of the stomach and a new set point that allows the successful reintroduction of oral intake. Others may argue that oral intake may be continued while on enteral nutrition, because partial gastric rest may already prove to be sufficient. In this respect, evidence in favor for stricter or more liberal gastric rest is lacking.

Conclusion

Following a stepwise treatment approach in gastroparesis, adequate symptom response was reached in 86% of patients, with weight gain in virtually all patients, independent of the symptom response. Diet and prokinetic treatment was effective in 58% of patients with gastroparesis. In decompensated patients, refractory to diet and prokinetic treatment, gastric rest with nasoduodenal tube feeding was effective in 47% and, in patients who failed all previous treatments, PEG-J appeared to be an efficacious alternative in 37% of patients. Despite the limited number of therapeutic options, a rigorous stepwise approach resulted in an acceptable success rate in tertiary referred patients with gastroparesis.

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Chapter 6

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Percutaneous Endoscopic Colostomy for adults with chronic constipation: Retrospective case series of 12 patients

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Abstract

Background

Percutaneous Endoscopic Colostomy (PEC) is a technique derived from Percutaneous Endoscopic Gastrostomy. When conservative treatment of chronic constipation fails, colon irrigation via PEC seems less invasive than surgical interventions. However, previous studies have noted high complication rates of PEC, mostly related to infections. Our aim was to report our experiences with PEC in patients with chronic refractory constipation.

Patients and methods

Retrospective analysis of all patients who underwent PEC for refractory constipation in our secondary referral hospital between 2009 and 2016.

Results

Twelve patients received a PEC for chronic, refractory constipation. Short-term efficacy for relief of constipation symptoms was good in 8 patients and moderate in 4 patients. Two patients had the PEC removed because of spontaneous improvement of constipation. Three patients, who initially noticed a positive effect, preferred an ileostomy over PEC after 1-5 years. One PEC was removed because of an abscess. Long-term efficacy is 50%: 6 patients still use their PEC after 3.3 years of follow-up. No mortality occurred.

Conclusion

PEC offers a technically easily feasible and safe treatment option for patients with chronic constipation not responding to conventional therapy. Long-term efficacy of PEC in our patients is 50%.

Introduction

A subgroup of up to 10% of patients with chronic constipation does not sufficiently respond to dietary changes, oral laxatives, rectal enemas or retrograde lavage (1-5). While retrograde colon lavage can be efficacious, it is time consuming (6) and often large volumes are needed, resulting in considerable patient discomfort. When all conservative measures fail, surgical treatments such as appendicostomy, ileostomy with colonic exclusion or segmental or total colectomy are considered (1-3, 5, 7-9). Previous reports demonstrate variable efficacy of these surgical treatment entities, morbidity of these procedures is high (7, 10-12). Less invasive and potentially reversible procedures such as sacral neuromodulation and tibial nerve stimulation have been disappointing with respect to efficacy (13-17). Therefore, exploration of potentially efficacious minimally invasive therapeutic alternatives for refractory constipation is warranted.

Percutaneous Endoscopic Colostomy (PEC), first described in 1986, is derived from Percutaneous Endoscopic Gastrostomy (PEG)(18). PEC enables antegrade lavage in case of chronic constipation, without the need for oral intake of large volumes of laxatives and the procedure is reversible (18-20). Remarkably, PEC is only rarely considered as alternative treatment for chronic refractory constipation. Only few studies have reported on efficacy and safety of PEC in chronic refractory constipation, mostly in case reports (18-23). These data are in favor of PEC, with moderate to good efficacy. However, there appears to be a barrier among clinicians towards placement, probably due to the considerable number of complications that have been reported (e.g. severe infections including fecal peritonitis), given the fact that the colon is involved.

Therefore, it has not become a widely applied technique. We believe that the role of PEC in the treatment of chronic refractory constipation is underestimated and underreported while the complication risks appear to be overestimated. The place of PEC in the therapy of chronic constipation especially versus more invasive surgical techniques considering efficacy, risk and reversibility, should be determined. Over the past years, we have used PEC in patients in whom retrograde colon lavage was no longer effective or was not tolerated by the patient. In addition, we describe the pull placement technique that is a simple and possibly safer variation potentially decreasing risk for complications. Aim of this study was to report our experiences with PEC in patients with chronic refractory constipation using the pull-technique known from PEG-placement and to position these experiences into perspective.

Methods

Study design and patients

After institutional board approval, a retrospective evaluation of all PEC placements performed for refractory constipation, between 2009 and 2016 was performed. Analysis of chronic constipation consisted of laboratory analysis (TSH (thyroid stimulating hormone), calcium), colon transit studies (radio-opaque marker test), and defecography, when the treating physician (LG) felt these were clinically indicated.

The radio opaque marker test involved the intake of 10 markers over a period of six days. Abdominal x-ray image was obtained on the 7th day. Slow colon transit was defined as a transit time >65 hours (calculated as: $2.4 \times$ the number of markers remaining in the colon).

PEC-procedure

All PEC procedures were performed by the same experienced gastroenterologist (LG). Bowel preparation was performed with bisacodyl 10mg two days before the procedure, and 2 liters of macrogols and electrolytes (Moviprep™; Norgine B.V., Hogehilweg 7, 1101 CA Amsterdam Zuid-Oost, The Netherlands). Before the procedure, antibiotics were administered intravenously (iv.) (amoxicillin/clavulanic acid 1000mg/200mg). Midazolam 5mg (iv.) was used for conscious sedation, combined with fentanyl 100mcg. During colonoscopy the colon was inflated with CO₂. Bowel cleansing was judged adequate in all cases (Boston Bowel Preparation Scale (BBPS) ≥ 2 for each segment). Transillumination was used to identify an appropriate puncture site in the ascending colon. Skin was infiltrated with local anesthetics, with puncture through the colonic wall. The anesthetic needle was held inside the colon with a jaw-forceps to prevent dislocation. A trocar was inserted after which the needle was removed. A guidewire was placed through the trocart and pulled endoscopically through the colon. PEC was then placed with the pull-technique (24) (Freka® PEG, Fresenius Kabi AG, 61352 Bad Homburg v.d.H. Germany). In addition, antimicrobial gazes (Antimicrobial Drain sponges, AMD, Covidien™: Excilon™ PHMB, 15 Hampshire Street, Mansfield, MA 02048) (25) were placed around the insertion site for three days with daily assessment for signs of infection (26).

Figure 1. View on luminal side of the PEC in transverse colon, with small hematoma due to local injection of anesthetics on the left side of the PEC.

Post Procedure

Antegrade lavage was started immediately with 500ml of lukewarm water per day. Antibiotics were continued orally for five days (amoxicillin/clavulanic acid 500mg/125mg). All patients were instructed to push and turn the tube daily, after one week (in which the fistula forms).

Data collection

Patients were discharged after one day and were seen at regular intervals to evaluate symptoms and therapeutic efficacy. Retrospectively, all patient files were examined, with a follow-up of 1-7 years (mean 3.3 years).

Outcome measures

Of primary interest was to assess improvement of constipation symptoms, determined by using a Global Physician Assessment Scale (GPA), as derived from Hanauer et al (27)(GPA 1: complete relief; GPA 2: marked relief; GPA 3: moderate relief; GPA 4: slight relief; GPA 5: no relief; GPA 6: worsening symptoms) based on the clinical effect reported by the patient at time of review at outpatient visit, six weeks after placement. Other parameters assessed were adverse events and requirement for surgery during follow-up. Patients were seen regularly with close follow-up. One of the authors (LG) has treated and followed all patients. All data were recorded by LG in the patients' files. Patients were instructed to report to the hospital and not to their GP or other healthcare provider in case of problems or complications.

Results

Twelve patients were included in the analysis (75% female, mean age 56 [range 28-70yrs]). Characteristics are listed in Table 1. A pragmatic approach towards diagnostics was followed. In patients with a clear clinical diagnosis (symptoms, digital rectal examination), appropriate conservative treatment was started. In unclear cases, defecography (6/12 patients) and/or radio-opaque marker studies (5/12 patients) were performed. Results of functional investigations are stated in Table 1. Conservative therapeutic measures consisted of oral laxatives and enemas, pelvic floor therapy (in case of pelvic floor dysfunction) and retrograde colon lavage. One patient refused retrograde lavage. PEC placement was technically successful in all patients, without adverse events during the procedure. Patients adjusted the amount and frequency of irrigation according to the effect (ranging from 500-1000ml per 1-2 days).

Effect

PEC placement and irrigation was effective in relieving constipation in all patients at short term follow-up (six weeks). Eight patients reported a good effect (GPA =1), four patients reported a moderate effect (GPA=2).

Complications

No major complications such as fecal peritonitis or bleeding occurred and mortality was zero. Minor peristomal infection developed in three patients, a small abscess developed in one patient (Table 2). These complications were successfully treated with oral antibiotics. Persistent abdominal wall pain occurred in two patients (16.7%), treated with local anesthetics. One PEC was replaced after two years because of a buried bumper, after which an abscess developed, which lead to a persistent colocutaneous fistula after removal of the PEC.

Long-term outcomes

At six months, efficacy of PEC treatment for alleviating symptoms was 66%. In six patients (50%), PEC is still in use (mean follow-up 3.3 years). Spontaneous improvement of constipation after 1-2 years resulted in removal of the PEC in two patients. Three patients, who initially noticed a positive effect, preferred an ileostomy over PEC after 1-5 years. These patients experienced too much discomfort from daily colonic irrigation (n=2) or deterioration of the effect (n=1). The fistula closed spontaneously in all three. As mentioned above, in one patient the PEC was removed because of abscess formation.

Table 1. Baseline characteristics

	M/F and age	RED +/-	Addi- tional diagnosis	Frequency of bowel move- ments prior to PEC (defeca- tion once per)	Radio opaque marker study	GPA 6 weeks after PEC	Results at long- term
1	F 73yr	-	-	7 days	Not performed	1	Removed due to complication
2	F 42yr	-	-	30 days	STC	2	Still in use
3	F 60yr	+	-	4 days	Not performed	1	Removed and received surgery
4	M 61yr	+	-	30 days	Normal	2	Still in use
5	F 49yr	+	-	3 days	STC	2	Removed and received surgery
6	F 63yr	+	-	7 days	Not performed	1	Still in use
7	F 55yr	-	-	5 days	STC	1	Removed due to relief of constipation
8	F 50yr	+	EDS-3	14 days	Not performed	2	Removed due to relief of constipation
9	F 32yr	-	EDS-3	7 days	Not performed	1	Removed and received surgery
10	F 72yr	+	-	5 days	Not performed	1	Still in use
11	M 56yr	-	Paraplegia	30-40 days	STC	1	Still in use
12	M 71yr	-	Paraplegia	7 days	Not performed	1	Still in use

STC=Slow Transit Colon (confirmed by radio opaque marker study)

RED=rectal evacuation dysfunction (as determined by evacuation proctography or physical examination)

EDS=Ehlers Danlos Syndrome.

- = no(ne)

GPA= Global Physician Assessment Scale

Table 2. Complications after PEC

Complication	N (%) Total N=12	Clavien Dindo classification (48)
Peristomal infection (treated with antibiotics, no PEC removal)	3 (25)	I
Abscess (treated with antibiotics, no PEC removal)	1 (8.3)	I
Persistent abdominal wall pain (no PEC removal)	2 (16.7)	I
Buried bumper (requiring PEC removal) and abscess with colocutaneous fistula	1 (8.3)	IIIa

Discussion

PEC is a potential alternative treatment option in patients with chronic constipation, when conservative treatment has failed. The procedure is reversible and does not exclude performing future surgical interventions. In our study population, treatment of chronic constipation with PEC had a moderate to good effect on symptoms and a low rate of adverse events.

Efficacy of this therapeutic intervention in our population for alleviating chronic constipation was 66% at 6 months, a result comparable to previous literature data (13,20). Long-term efficacy is considerable (50%), especially when taking into account the refractory nature of symptoms. To our knowledge, this is the first reporting on longer term efficacy (mean 3.3 years) of PEC for chronic constipation (19, 21). In our group, two patients (16.7%) experienced spontaneous relief of constipation. This is an argument in favor of careful evaluation of chronic constipation and of being restrictive in referral for surgery.

With respect to minor infectious adverse events, our study showed rates (33%) comparable to previously reported data (18-77%) (18, 19, 21, 23). Tube removal due to infection or abscess was necessary in one patient (8.3%), in contrast to 44% of the reported rates (19). Fecal peritonitis is a major issue in PEC, considering the abundance of resident colonic microbiota. We did not encounter fecal peritonitis in any of our 12 patients whereas this has been reported in 9-12% of patients previously (18, 19). We believe that the regimen with use of antibiotic gazes in addition to systemic antibiotics may have contributed in preventing fecal peritonitis (26).

Our mortality rate was zero, contrary to literature data where high rates have been reported, up to 26% (19). A recent study on this topic described 19 patients with a one-year follow-up period. Pain occurred in 47% of patients, which led to removal of the tube in 26% (21). We observed pain in only 16.7% of patients. We believe that this discrepancy can be explained by the technique used for PEC placement. The PEC technique used by Duchalais et al. and Moriwaki et al. includes insertion of anchors to fixate the colon to the abdominal wall, thereby potentially increasing the risk for infections and pain, and making the technique more difficult (success rates reported of 90%)(21, 28). The pull-technique we used is based on a procedure that most endoscopists who perform PEG placements are familiar with. Baraza et al. and Cowlam et al. also used this technique but held the needle in place with a snare, while in our opinion a grasping forceps provides better stability (18, 19). Previous studies using the same pull technique had significantly higher complication rates but included lower numbers of patients with constipation (the primary indication being volvulus) (18, 19). In addition, previous studies did not report use of antibiotic gazes, and applied a shorter post-procedural antibiotics period (8 hours instead of 5 days)(18). Lastly, previous studies reporting on the use of PEC in cases of both constipation and volvulus or pseudo-obstruction report on lower mean age in patients with

constipation (mean age 41-51 years) compared to patients with intestinal pseudo-obstruction and recurrent sigmoid volvulus (mean ages resp. 70-75yrs and 79-80yrs). Higher ages were also reported by other studies on pseudo-obstruction (1, 29, 30) and volvulus (31, 32). Mean age of our population was 56 years, significantly younger and probably less frail than the patients undergoing PEC for volvulus or pseudo-obstruction. Our patients all were in good nutritional state and general condition before PEC, which might also contribute to the lower number of complications. On the other hand, complications in the studies by Cowlam and Baraza did not differ amongst groups, despite the age difference and frailty of the elderly groups (18, 19).

Compared to surgery, PEC is less invasive and reversible. It therefore has the potential to become a more attractive alternative, when more data become available on efficacy and complications. Surgical procedures for chronic refractory constipation include total colectomy with ileorectal anastomosis, and subtotal colectomy with ileosigmoid/cecorectal anastomosis (7, 12). Mean success rate for these interventions is reported to be high, around 89% (7). However, postsurgical adverse events are described in up to 45% of patients (10, 11). In addition, mortality is considerable when an anastomosis is made (10). Subtotal and segmental colectomy often fail to improve symptoms, which might be due to the presence of a more generalized motility disorder or co-existing pelvic floor disorders (5). After total colectomy, functional outcomes vary; constipation persists in 8-30% of patients (11, 21, 33, 34). Others have reported better outcomes with 79-90% of patients having satisfactory results (35, 36), see Table 3.

Table 3. Comparison of available treatments

	PEC (current study)	PEC (previous studies)(18, 19, 21, 28)	Colectomy with ileorectal anastomosis or ileostomy (7, 40-42, 49, 50)	Malone stoma (6, 43-46)	Transibial stimulation (13-15)	Sacral Neuro-modulation (16, 17)
Efficacy – initial (<8 weeks, response rate)	67% Good 33% Moderate	Not reported	Not reported	Not reported	26%	28%, no significant difference vs placebo condition
Efficacy – long term (response rate)	50%	50-75%	64-94%	25-75%	12-32%	23-25%, no significant difference vs placebo condition
Morbidity	33% Minor infection 16.7% Minor pain 8.3% Buried bumper	18-77% Infections 9-12% Fecal peritonitis	53.4% (total), Re-surgery due to complications; 9% Small bowel obstruction 12% Ileus 9.5% Diarrhea (ileostomy)	30% (stenosis, occlusion or spontaneous closure)	0-10.5% (mild pain and oozing bleeding)	44% Pain 16% Wound infections 23% Urological adverse events (e.g. urinary tract infections) 61% Total
Success rate (procedure)	100%	90-100%	89-100%	77%	100%	100%
Easily reversible	Yes	Yes	No	Yes (requires surgery)	No	No

Total colectomy with ileostomy (definite or temporary) appears to be the surgical procedure of choice (8, 9, 37-39). However, after ileostomy, complication rates of 53.4% (with re-surgery in 29.3%) are reported (40). Constipation persists in 4-15% of patients (40, 41), with up to 50% needing further surgery (7, 11). Moreover, ileostomy might also lead to diarrhea (9.5%) (42).

Another surgical option is the Malone procedure (appendicostomy)(43). Limitations of this procedure are stenosis, occlusion and spontaneous closure of the appendicostomy. These complications have been observed in 30% of cases (6, 44, 45). Success rates of around 70% have been reported (46). The Malone procedure is considered an alternative therapy for patients with high operation risk (7). Cannulation is necessary for lavage and leakage may occur. Clinical outcomes vary greatly, with up to 75% requiring colostomy/ileostomy (44, 47).

We therefore believe that PEC (placed using the pull-technique described here), given its high success rate for placement, considerable long-term success rate of 50% and low rate of major complications, should have a place in the treatment algorithm of chronic refractory constipation, potentially filling a gap between conservative and surgical treatment options. In terms of efficacy, PEC success rate is comparable to the Malone procedure, but PEC is characterized by less complications and higher success rate for placement. The limited number and severity of complications in addition to its reversible nature are in fact the primary advantages of PEC compared to more invasive surgical interventions, even when PEC appears less efficacious on long-term. Therefore, PEC seems particularly attractive for patients with a high perioperative risk or generalized gastrointestinal motility disorder.

Limitations of our series are the retrospective nature of the study, the small number of patients, the lack of patient reported outcome measures, and the fact that the exact etiology of their chronic constipation was not investigated systematically in all patients. Our study should therefore be considered as exploratory. Future studies will have to investigate more patients' characteristics in order to determine which patients might benefit from this form of treatment.

Conclusion

We postulate that PEC deserves more attention and a more prominent place in the treatment algorithm of otherwise therapy resistant chronic constipation. PEC, when applying the pull technique as used for PEG placements, seems to be a safe, easy to perform and is a reversible endoscopic alternative for surgical interventions in patients with chronic constipation, with reasonable long-term efficacy.

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GENERAL DISCUSSION AND CONCLUSIONS

General discussion and conclusions

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Background

Since its development and introduction into clinical care in 1980, PEG has gained popularity over the past decades into the method of first choice for providing an enteral access for long-term enteral feeding (≥ 30 days) (1-4). Despite its availability for almost forty years, some issues remain unclear or are not widely known. With this thesis we aimed to fill these gaps in knowledge around PEG for nutritional support and for other applications, and to answer clinical relevant questions on this procedure. We aimed to stratify and simplify the decision process in choosing the most eligible treatment for each individual patient, and to provide an overview of the place of PEG in different treatment algorithms.

We compared PEG with its radiologic alternative PRG (**Chapter 2&3**), provided new insights on complications in PEG (**Chapter 4&5**), and described alternative applications (specifically the role of PEG-J in gastroparesis (**Chapter 6**), and the place of PEC in chronic constipation (**Chapter 7**)).

PEG versus PRG

Beside Percutaneous Endoscopic Gastrostomy (PEG), Percutaneous Radiologic Gastrostomy (PRG) is commonly used in clinical practice. Outcomes of both techniques have previously been reported, however implications of these results are limited due to small sample sizes and high risk of bias (5-11). As a consequence, consensus on which technique is more favorable has not been reached up to now.

In **Chapter 2&3**, we aimed to extensively compare PEG and PRG, in a systematic review and meta-analysis (**Chapter 2**) and a study of the largest group of patients to date (**Chapter 3**).

Based on previous literature we expected comparable mortality (with differences for various indications such as MND or HNC), higher infection rates in PEG, and more tube related complications in PRG (7, 12-14).

The meta-analysis performed in **Chapter 2** showed no differences in mortality and infectious complications between PEG and PRG for the entire population. As expected, a higher rate of tube related complications was found after PRG. Although these tube related complications are mostly not severe (e.g. dislocation, obstruction), they account for hospital visits with significant burden for patients.

Surprisingly, similar rates of infectious complications were seen for PEG and PRG. We hypothesized that this would be due to antibiotic use in PEG awhile no antibiotics are used in PRG. However, many studies followed the same antibiotic policy around both procedures. When analyzing infections in studies not using antibiotics in PRG, no differences in the overall result was seen.

Subgroup analysis revealed higher procedural related mortality after PRG in head and neck cancer (HNC) patients. This was due to higher peritonitis rates after PRG. However, only three studies could be included in this subgroup analysis, therefore these results should be interpreted with utmost caution. Previously, meta-analyses comparing PEG and PRG have been performed (7, 12-14). Nevertheless, several differences are present when comparing the results of our analysis to previous meta-analyses. This can be explained to certain extent by differences in study design and methodology, as described in **Chapter 2**.

We consider our results, based on low heterogeneity and symmetric funnel plots, as more reliable compared to other meta-analyses. It should be acknowledged that randomized data are not available on this topic, therefore limiting interpretation of results of our study and of others. Besides that, studies were relatively small in sample size, the largest being 370 patients in total (5). In our opinion, a more extensive comparison of procedures is warranted.

Chapter 3 describes an extensive single center comparison of 760 patients with either PEG or PRG. We hypothesized that by comparing complications between PEG and PRG in relation to indications, we might be able to predict which technique is best for an individual patient. Our data showed results similar to **Chapter 2**, with comparable procedure related mortality, and 30-day mortality mostly related to the underlying disease.

One of the findings with high clinical impact in **Chapter 3** was the high rate of 30-day mortality after both procedures, mostly in patients with a very poor condition, e.g. shortly after major CVA. These patients appeared to have a high risk of early death or aspiration pneumonia. We therefore strongly advise to avoid or delay gastrostomy placement in these patients and start with nasogastric or nasoduodenal/-jejunal (in case of aspiration risk) feeding as a valuable alternative. This should also be considered in patients in which life expectancy or prognosis is difficult to estimate. After at least four weeks, the condition and prognosis of the patient can be re-evaluated for placement of a gastrostomy. In daily practice, we regularly encounter requests for PEG in a very early phase, that is without prior nasogastric or nasoduodenal feeding. A prospective trial will help to more precisely determine the best timing for PEG placement.

In this manner, unnecessary risks of (early) gastrostomy placement can be avoided.

Aspiration pneumonia occurs more frequently in vulnerable patients. Of note is that in our experience, aspiration is often seen as a reason to order a gastrostomy. However, this should not be seen as a valid indication, for the risk of aspiration is not lower with a gastrostomy or nasogastric tube (15-17). In those cases, more distally placed tubes such as duodenal or even jejunal tubes should be considered. These new insights advocate for a counseling role of the gastroenterologist including a thorough consideration whether or not PEG placement is suitable. In current practice, the PEG is regularly ordered by other specialists who often are not fully aware of the procedure and other related risks.

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On the other hand, some patients are not offered PEG because it is seen as a too high risk procedure. This appears to be the case in ALS and in patients with Parkinson's disease. In our practice the 30 mortality in patients with ALS (**Chapter 5**) receiving a PEG was zero and this was also true for patients with Parkinson's disease receiving Duodopa via PEG-J (non published data).

Another important finding was the high rate of tube related complications in PRG compared to PEG. Replacement due to dislocation or occlusion accounted for extra consultations. Beside these complications, regular replacements of PRG tubes are necessary. With these data combined, a mean of 2.1 tubes per patient was observed compared to 1.3 tube per patient in PEG. As a side note, PRG tubes were placed prophylactically in 62.6% of patients, and often only in place or used for a few months (versus only 22.6% of PEG patients), still leading to a higher number of replacements.

Another quite remarkable finding was a case of tumor seeding, occurring after PRG. PRG is often chosen as treatment of choice in case of oropharyngeal or laryngeal carcinoma because it is believed that PEG could contribute to metastasis at the insertion site due to sweeping tumor cells by pulling the PEG-tube during insertion. Metastasis at the insertion site after PRG has only been described once before (18) and was therefore an unexpected complication. A patient with cT3N2bMx laryngeal carcinoma underwent radiologic PRG placement (standard procedure). Three weeks later, the PRG fell out and was easily replaced through the existing fistula. Another three weeks later, the stoma site showed an irregular aspect and bled easily. After four months with two changes of the tube and use of silver nitrate, surgery was performed to excise the granulation tissue. Histological examination showed a metastasis of the previous laryngeal squamous cell carcinoma. At that time, lung metastases were present as well.

This case of tumor seeding after PRG is not in line with the concept of sweeping tumor cells to the insertion place. It points to less well known ideas and concepts behind the mechanism of tumor seeding. First, hematogenous spread is a plausible option, supported by the concomitant lung metastases in our patient. Secondly, implantation of tumor cells at any wound site in contact with the digestive tract after swallowing them with saliva, might contribute as well. Pulling the tumor cells along with the gastrostomy tube did not occur in this case and can therefore not be the explanation, as previously suggested by many authors (18-22).

Reporting and publication bias should of course be considered as underlying cause for the low reported number of tumor seeding in PRG in literature, as negative outcomes are less likely to be reported and published (23). On the other hand, the difference between PEG and PRG seems significant, with 49 cases known in PEG versus 2 in PRG at this time (18-22). Therefore, the odds point

to PEG as having a higher risk for tumor seeding than PRG in obstructing oropharyngeal tumors, however we postulate that further research is necessary before a firm conclusion can be drawn.

In case gastrostomy is required in non-oropharyngeal HNC, or after treatment of the tumor, in our opinion PEG would be the better choice for the lower number of complications we found.

The relatively low number of infections might be due to underreporting, in our opinion. Ideally, patient data ought to be collected prospectively to provide a more complete overview of these minor complications. Because of the retrospective nature of the current study, such data were not available. We believe that these complications remain underreported, as general practitioners usually treat these. In case of other, less common or more complicated problems, patients and/or general practitioners contact the hospital.

Other alternative options to PEG, when PEG is not possible or not considered safe, are push-PEG, Peroral Image guided Gastrostomy (PIG), or Percutaneous Transesophageal Gastrostomy (PTEG). These procedures are not regularly performed in our centers and therefore no reliable comparisons can be made. Literature data suggest similar infection rates but higher tube related complications (10-12%) with push-PEG, however reported rates are lower than in PRG (24, 25).

PIG, as described before, might be a promising option, however experiences are limited (26).

PTEG can be used in cases of gastrectomy or massive ascites. However, only small case series have been reported, and the technique is not widely known (27-31). We feel experience is required to perform this technique in which the esophagus is punctured via ultrasound guidance. We certainly do not recommend this to gastroenterologists without a specific training, even in endoscopists familiar with PEG placement.

In daily practice, choosing between PEG or PRG should be dependent on local expertise and availability of both techniques. The underlying disease and condition of the patient determine the risk of complications in general. In some patients, placement of a nasogastric/duodenal tube would be sufficient and safer. Therefore, all factors described above should be taken into account in the decision process for each individual case.

Conclusion

In conclusion, PEG is in our opinion the first choice treatment because of the above stated reasons, besides in certain cases including oropharyngeal carcinoma (before surgery), stenotic or narrow esophagus, or when sedation is not possible. In those patients, PRG is a valuable alternative, even if this includes referring patients to another hospital. Indications, timing and type of gastrostomy (PEG

or PRG) should also be known by referring specialists such as neurologists, otolaryngologists, etc. However, a multidisciplinary approach is important, including the advice of the gastroenterologist. Push-PEG and PIG are promising however not regularly used in most hospitals. We recommend only experienced endoscopists perform these techniques. The same considerations apply to PTEG, which has shown promising results but is very rarely used. Besides that, the cosmetic aspect is a major disadvantage in our opinion, and we expect much lower percentages of successful placement, and often endoscopic assistance is required besides the fluoroscopic procedure (30% of 30 patients in the study by Murakami et al (32)). However, Udomsawansup et al. reported successful fluoroscopic placement in 94% of 17 patients (30).

Complications of PEG

PEG placement is safe and well tolerated in the majority of patients. However, complications may occur; reported rates vary (overall reported rates between 4.9% and 40% (2, 33, 34)) depending on patient selection, study design and structured follow-up or not. The majority are minor complications, with major complications occurring in 0.4% to 5% (33).

Close follow-up is indicated, including assessment of the surrounding skin, location of the tube, approximation of the tube to the abdominal wall, and avoiding excessive traction on the PEG.

In the next paragraph an overview of complications and risk factors is presented, based on current literature, in order to attribute to the acknowledgement on this subject, and thereby helping the endoscopist to choose the best option for individual patients.

Periprocedural complications

Periprocedural complications are mostly respiratory, such as laryngospasm, aspiration, respiratory depression or apnea, desaturation or airway obstruction (35). Aspiration during the procedure is reported in approximately 0.3-1.0% of cases (36-38). Serious cardiorespiratory complications as a result of sedation were reported in 0.5% of patients in a large US survey (39). Numbers of other periprocedural complications are rarely reported, however it seems plausible that this is due to reporting bias.

Pneumoperitoneum

Microperforation of the peritoneum and thereby occurrence of a pneumoperitoneum is reported in up to 56% of cases (3, 40). It is mostly clinically irrelevant, unless other signs of peritonitis are present (41). A large study of 722 patients by Blum et al. reported an incidence of 5.4%, of which 85% was managed conservatively, with peritonitis occurring in most other cases (42). However in an ICU population, pneumoperitoneum was related to an increase in major complications and 30-day mortality (43), but on the other hand not related to any other complications in a second study (44).

As a sidenote, the question arises whether pneumoperitoneum does not occur in every patient. By puncturing the stomach and abdominal wall, the peritoneum is punctured. Due to higher pressure in the stomach during the endoscopy, some leakage of air will most likely occur in all patients ('pneumoperitoneum'). No clinically relevant pneumoperitoneum has occurred in our patients (**Chapter 3, 4, 5**).

Post procedural complications

Post procedural complications are divided into early (≤ 30 days) or late (>30 days) and classified as minor or major (2, 3).

Infectious complications

The most common complication after PEG is *site infection*, reported at rates between 8-30% (one study even 47%)(2, 45). Part of the infections are believed to occur by translocation or oropharyngeal bacteria to the insertion site with pulling the tube. Therefore, in push-PEGs, the number of infections might be lower, however only limited evidence is available supporting this case (45-47). Shastri et al. showed no differences in wound infection after push-PEG comparing antibiotic prophylaxis vs. placebo, with an infection rate of 19.2% vs. 21.7% (47). Neither did we find differences in our analysis (**Chapter 3**), but it should be acknowledged that we included only seven patients with push-PEG in our study.

In case of wound infection, culturing the insertion site is not proven to be helpful in general. Removal of the PEG is not necessary if a proper antibiotic response is seen (33).

A severe infection might progress into *peritonitis*, with reported rates around 1-2% (2, 48). Peritonitis can also be caused by leakage of gastric contents, e.g. in case of premature removal of the tube, or in case the fistula has not formed yet. The tip of the catheter might then migrate into the peritoneal cavity. Antibiotics are necessary and tube feeding must be discontinued (4, 36, 49). Low rates of peritonitis were seen in our study population (1.2% in one group (**Chapter 4**), and no peritonitis occurred in the group described in **Chapter 3**).

Rarely, a *necrotizing fasciitis* develops ($<1\%$), presenting with edema, erythema, local bullae, and systemic spread. Immediate removal of the PEG is required, as is surgical debridement and treatment with antibiotics (50, 51). Patients with delayed wound healing (e.g. with a poor immune system, malnutrition, wound infections, and Diabetes Mellitus (DM)) are at risk (52). No necrotizing fasciitis occurred within our study population.

In **Chapter 4**, a new method of preventing peristomal infections in PEG was described. We found an infection rate of 9.4% using only bactericide gazes after PEG placement. No intravenous or oral antibiotics were administered. Use of these gazes in preventing PEG site infections has never been described before. Use of systemic antibiotics prophylaxis did significantly lower infection rates in previous studies, with a reported rate of 9.4% in a meta-analysis (45, 53). So, the use of gazes instead of systemic antibiotics is a patient-friendly alternative with lower costs and similar infection rates.

A serious drawback of our study was the lack of structured follow up and structured collection of clinical data. The classification of peristomal infection and need of antibiotic treatment was classified by expert gastroenterologists. In the future, an infection score to classify the need of antibiotic treatment might provide a more homogenous classification and follow up. Nevertheless, we believe that expert opinions as we have used are a valuable and precise measure to classify infection.

An interesting finding was the low number of infections (4%) in a group of patients who were on antibiotics for other reasons prior to PEG (e.g. urinary tract infection). The question whether a combined infection prophylaxis of systemic antibiotics with antibiotic gazes would serve as best practice, remains. This could be subject of further research, although large numbers of patients are required to reach an adequate study power, taking into account, the expected low infection rates. Regarding the number of PEGs placed in our hospitals (around 70-80 per year), such a study would take over ten years to perform, even if it were a multi-center trial.

Aspiration pneumonia occurs in the majority of patients within the first two weeks after placement (3). Otherwise, it should not be considered a post-procedural complication in our opinion. We found rates of 0.9% and 2.1% in our population, and no aspiration pneumonia in the ALS population (**Chapter 3, 4, 5**).

Fixation related complications

Peristomal leak might occur if the external bolster is fixed too close or too loose to the abdominal stomach wall.

Tight placement of the external bolster impairs blood flow and aggravates the risk of infection, ulceration, and decreases wound healing. A 1cm distance between the external bolster and the skin creates enough tension to ensure proper healing of the tract and prevents compression (3, 54, 55).

Fixating the external bolster too tight may lead to *Buried Bumper Syndrome (BBS)* as well. The bumper erodes in the stomach mucosa due to excessive traction, which can be seen with endoscopy. Back in 1986, Ponsky already advised to prevent excessive cannula traction (56). In 1990, the term 'Buried

Bumper Syndrome' was introduced by Klein et al. after numerous cases of retraction, migration, impaction or extrusion were reported (57). The estimated incidence of BBS is 0.3-2.4% (58, 59), comparable to rates we described (1.4% and 0.9%) in respectively **Chapter 3&4**. A buried bumper causes pain and prohibits proper feeding, due to obstruction of the tube. Therapeutic options consist of extraction, mostly after cutting the overgrowth tissue with for example a needle knife or a papillotome (59, 60).

After that, a balloon-PEG (also known as 'Mic-Key button') can be placed to prevent BBS (61).

Bleeding

PEG is considered a high-risk procedure on the behalf of bleeding complications (62). It is rare to occur (1-2.5%) due to precautions regarding e.g. anticoagulants as described in the first part of this thesis. Bleeding is mostly mild, requiring only pressure to the insertion site. Performing a re-endoscopy is rarely necessary, as is the case with surgical interventions. Massive bleeding has however been described, mostly due to iatrogenic trauma to the epigastric artery, local infection, or pressure necrosis with erosion into the artery (63-65). In both our study groups (**Chapter 3 and 4**) bleeding rates occurred at 2 respectively 2.1%, in one patient being a fatal gastric bleeding (0.3%).

Tumor seeding / gastric site metastasis

A major complication following gastrostomy insertion is tumor seeding, or metastasis to the stomal site. The first case has been described in 1989. Since then, 49 cases have been reported in literature, with a <1% estimated incidence (19-22).

Local site metastasis was found in 9.4% of pull-through PEG patients with esophagus squamous cell carcinoma in a study by Ellrichmann et al. (66). Several mechanisms have been described, but no clear evidence is present. The first theory is iatrogenic spread of tumor cells by pulling the PEG past the tumor at insertion. Secondly, lymphatic or hematogenous spread is assumed because of the high incidence of concurrent metastasis, with seeding to a wound because of the opportunity of adhesion over there. At last, desquamation of tumor cells with swallowing them, and adhesion to the PEG tube site wound, is presumed to be an explanation (19-22). These last two theories are supported by our report of tumor seeding after PRG placement in **Chapter 3**, whereas no tumor seeding after PEG occurred.

Tube related complications

Chapter 3 and 4 showed low rates of tube related complications, occurring mostly in PEG-j patients. The jejunal extension was more prone to dislocate (and migrate to the ileum/colon) than the regular PEG (with a total dislocation rate of 6.5% at short and long-term combined in **Chapter 3**). In **Chapter 4**, dislocation occurred in 4.2% of patients, mostly in patients with PEG-j. Literature reports an even

higher rate, up to 36% (67-69). Besides that, obstruction of the extension might occur due to its smaller diameter than a regular PEG tube, occurring in 2.3% of our patients in total. Previous studies report rates of 3.5-35% in PEG-j tubes (69-71).

Gastric outlet obstruction

Migration of the PEG tube and thereby obstruction of the duodenum is rarely described and did not occur in any of our patients. It is preventable by properly positioning the external bolster to prevent migration from the abdominal wall (34).

Other rare complications

Many case reports appeared in the last few decades considering rare complications. These include duodenal bulb perforation (72), necrotizing candida infection (73), retrograde intussusception (74), acute gastric dilatation (75), duodenal paralysis (76), mediastinitis (due to perforation of esophagus) (77), bowel looping around PEG (lead to volvulus)(78), liver injury(79), gastrohepatic fistula (due to dislodgement of PEG)(80).

Mortality

Procedure related mortality

Procedure related mortality rates are low, with reported rates around 0-2%, in the majority of cases due to aspiration pneumonia or peritonitis (5, 13, 81-85). In **Chapter 4** a rate of 0.9% is found, **Chapter 3** (with a rate of 1.7%) shows this seems mostly related to the underlying condition of the patient, and that it might be preventable by careful patient selection.

30-day mortality

30-day mortality rates vary greatly, from 0-1% to 43% (13, 82, 86), mostly depending on the condition of the patient prior to PEG (84, 85, 87), as shown in **Chapter 3** as well. A nationwide survey in the United Kingdom even revealed a 69% mortality within 2 weeks and a 6% procedure related mortality. However, underreporting of procedures is expected in this survey, therefore these data are probably not completely reliable. 30-day mortality rates differ amongst subgroups, with rates of 3-15% reported in MND (83, 88-90). Abuksis reported a 30-day mortality of 72% in hospitalized patients (91). In HNC, rates of 0-1% are reported (13, 82, 86).

Better patient selection prior to PEG has been advocated before (92) and is strongly supported by our results in **Chapter 3**.

Tanswell et al. postulated that assessment by a multidisciplinary nutrition team before PEG placement could reduce early mortality. In their sample, one-week mortality dropped from 10-20% to 0% after

careful assessment of the patients' comorbidities, wishes, and selection based on indication for PEG (93).

Complications in patients with ALS

Chapter 5 describes complications after PEG placement in a vulnerable patient group, i.e. patients with ALS. Use of conscious sedation during PEG placement without NIPPV is described for the first time. No respiratory complications were seen, not periprocedural nor post-procedural. Half our patients (51%) had moderate to severe pulmonary dysfunction, indicated by an FVC <70% resp. <50%. Even in this group conscious sedation during PEG placement was safe. Previously, FVC was shown to not influence survival after PEG (as as side note, NIPPV and general anesthesia were used there, so results are not completely comparable to our study)(94).

However, we advise to explore measurement of lung capacity in another way in the future. The use of a CO₂ based measurement seems more accurate in our opinion. This has to do with both the difficulty of the enclosement of the mouthpiece (due to muscle weakness), and the question whether or not forced expiration is necessary during PEG. Capillary blood gas measurements would also be optional to provide these data.

In daily practice, we believe that in ALS patients, even with moderate pulmonary dysfunction, conscious sedation in PEG should be considered. We have treated only a few patients with severe pulmonary dysfunction, in none of them complications occurred. However, more research in this group is needed to confirm our results. Besides that, the use of propofol sedation is of interest, especially in ALS patients, due to the shorter effect, better titration and more controlled sedation (94). Alternatively, PRG's could be placed, for sedation is not necessary during PRG. Our meta-analysis (**Chapter 2**) shows no differences in complications or mortality between PEG and PRG in a subgroup analysis of ALS patients.

Risk factors for complications

Over the years, many risk factors for complications and mortality after PEG placement have been identified. Knowledge of these factors is helpful in the decision whether or not to place a PEG in a specific patient. In our studies, we found underlying disease and more specifically the condition of the patient before placement, to be risks factor (**Chapter 3**). Procedure related complications occurred in patients with a very poor condition and/or severe comorbidities (e.g. liver cirrhosis, vascular dementia). CVA was a risk factor for 30-day mortality (OR 5.190 [2.139-12.597]).

Whereas higher BMI was (borderline) protective for 30-day mortality, age and comorbidities (such as DM, cirrhosis, cancer, COPD) were not identified as risk factors for 30-day mortality in our analysis. Our study in ALS patients (**Chapter 5**) did not show use of sedation or neurologic impairment to be risk

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factors for aspiration. In **Chapter 3**, CVA was present in many patients with aspiration pneumonia (but was not statistically significant).

Previous literature has reported on all these factors as being predictive factors for 30-day mortality (95-99). All risk factors currently identified are stated in Table 3.

In conclusion, complications after PEG should be taken very seriously and precautions to prevent them should always be taken. Although PEG has been used for almost forty years, more research is warranted to aid us in patient selection.

We strongly advocate a universal system for placement of PEG, starting with a standardized intake-procedure which helps in estimating the risk of placement. This should include questioning the estimated condition and prognosis, comorbidities, weight/BMI, use of medication, medical history. Contra-indications should be clearly stated, as described in the introduction part of this thesis (table 2). For relative contra-indications, the clinician should consider placement per individual case. As described before, former strict contra-indications such as ascites, VP drain, obesity and previous abdominal surgery, have been studied and similar complication rates as 'normal' patients have been reported. Therefore, placement might be considered in these cases but should be based on experience and the condition of the patient. Ideally, an algorithm as described below (Figure 3) should be incorporated to provide an advice on placement.

The placement itself should be performed as described before. More specific techniques such as push-PEG, PEJ or PEC should only be placed by an experienced endoscopist in specific cases.

A registry of follow-up and complications, which is being used for many other procedures at this time in the Netherlands, seems justified for PEG and PRG due to relatively high risks and complication rates. One control should take place 30 days after placement. Long-term follow-up would be of interest as well, mostly for complications such as tube dislocation and buried bumper.

Ideally, all reported data should automatically be transferred to a national system in order to prevent reporting bias, which could occur if complications have to be reported in a separate system.

Such a universally accepted and implemented system would allow us to collect many more data. Specific points of improvement would be easy to observe and execute in a PDCA cycle. On the longer term we believe that many complications of PEG/PRG are preventable and truly can be avoided.

Table 3. Identified risk factors for complications in PEG

Complication	Identified Risk factors
In general (poor outcome) (100, 101)	<ul style="list-style-type: none"> • Age ≥ 75 years • ASA class IV • Malnutrition with BMI < 18.5 • Ongoing antibiotic therapy • Albumin count ($< 28\text{g/L}$) • Placement of the internal bolster at the upper body of the stomach • High leukocyte count • Inexperienced endoscopists
Aspiration (102)	<ul style="list-style-type: none"> • Supine position • Use of sedation • Neurologic impairment
Infection (48, 103)	<ul style="list-style-type: none"> • Delayed wound healing: <ul style="list-style-type: none"> ◦ Diabetes Mellitus ◦ Immunosuppressive medication ◦ Low immune status ◦ High leukocyte count ◦ Poor nutritional status • Liver cirrhosis • Malignancy • Exposure to radiotherapy
Necrotizing fasciitis (104-106)	<ul style="list-style-type: none"> • Diabetes mellitus • Malnutrition • Immunosuppression • Chronic renal failure • Pulmonary tuberculosis • Alcoholism • Wound infection
Bleeding (3, 33, 62)	<ul style="list-style-type: none"> • Use of anticoagulants (acenocoumarol, fenprocoumon) • Use of P2Y₁₂ receptor antagonists (clopidogrel, prasugrel, ticagrelor) • INR > 1.5
<u>Mortality</u> Procedure related mortality (104)	<ul style="list-style-type: none"> • C-reactive protein (CRP) $> 21.5\text{mg/L}$ combined with serum albumin levels • $< 31.5\text{ g/L}$

Complication	Identified Risk factors
30-day mortality (95-98, 104, 107)	<ul style="list-style-type: none"> • Higher age • Lower BMI (own results as well) • CRP > 21.5mg/L • Diabetes Mellitus • Albumin <30 g/L • Cirrhosis • Cancer • COPD • Residing in a nursing home • Urinary tract infection combined with history of aspiration and age > 75yrs • CVA (own results)

The role of PEG-J in gastroparesis

Chapter 6 focused on a different application of PEG, describing the role of PEG-J in the treatment algorithm of patients with gastroparesis, studying a cohort of tertiary referral patients. Treatment of this severely invalidating condition has shown to be difficult and has a significant influence on Quality of Life (108-110).

Enteral feeding (with or without gastric rest) is necessary in approximately 30% of gastroparesis patients (111). Although PEG-J is advised as first choice to provide enteral feeding, experiences with respect to outcome and complications have never been described. Only data on surgical jejunostomy (112, 113) and PEJ (114, 115) have been reported, but only with respect to complication rates. Therefore, our analysis reporting on subjective and objective outcomes provides more insight in the placement of PEG-J in the treatment of gastroparesis. We have described the stepwise approach used in our center. This approach can be used as a practical guideline for nutritional interventions in gastroparesis.

We propose to adhere to this approach in all gastroparesis patients. Initially, dietary advice should be given, with addition of erythromycin when necessary (with rotated cycles, maximum four consecutive weeks of medication). If not effective, domperidone or metoclopramide can be tried. We advise a maximum of 6 weeks of evaluation per medicine. In case no effect is seen, Gastric Rest should be considered for three months. If thereafter no symptom response is obtained and oral intake cannot be fully restored a PEG-J should be the subsequent step. We advise to take time to evaluate the effect of oral reintroduction for at least 8-12 weeks, providing that weight loss is not a major issue. A prokinetic might be added if no satisfactory symptom response is obtained.

If no effect on symptoms is seen after 3-6 months, other treatments (Table 4) can be considered.

Literature data on PEG-J, PEJ, PRJ and surgical jejunostomy in gastroparesis

Our study showed high procedural success rates (100%) and no major complications, the only complications we found were buried bumper (16%) or dislocation of the jejunal extension (32%). High major complication rates are reported for alternative options such as surgical jejunostomy or PEJ (range 18-53%)(113, 115). PEJ also showed lower procedural success (78.6%)(115).

In the future, more data on gastric rest should be collected, for the actual effect on symptoms and weight has never been evaluated. Our data need confirmation by other groups. We applied a strict regime of complete gastric rest for three months, based on personal experiences. No data are available comparing this complete GR to a more liberal approach continuing oral intake next to nasoduodenal feeding.

As described before, other treatment options are available for patients who do not respond to all interventions including PEG-J.

A potential treatment is the intrapyloric injection of botulinum toxin. This is known for high costs and low symptomatic response and is therefore currently not recommended by the American Gastroenterological Association (AGA)(117-119). It is still applied clinically in severe and otherwise therapy refractory cases, due to lack of other alternatives.

Recently, several new, alternative treatment options have become available for refractory gastroparesis. Endoscopic placement of a stent through the pylorus (i.e. transpyloric stenting) improved symptoms and gastric emptying in a series of 30 refractory gastroparesis patients (120, 121). Stent migration and short-term durability are however limitations of this modality, which underlines the need for additional research. Second, Gastric Per-Oral Endoscopic pyloromyotomy (G-POEM/POEP) has evolved and results of the first cases are very promising. A recently published retrospective analysis in 29 patients described a clinical success rate of 70% at six months follow-up and two severe complications occurred (i.e. postoperative bleeding and peritoneal abscess)(122). Additional (preferably prospective and controlled) studies are necessary to determine the safety and long-term durability (123-127). Surgical pyloroplasty is a more invasive treatment option with reported symptom improvement in 83% of patients after one month follow-up, and normalization respectively improvement of gastric emptying in 71% and 96% (128, 129). Despite the lack of randomized controlled trials, these results are promising and adverse event rates were low (130).

Figure 1 shows our stepwise approach in the treatment of gastroparesis.

Table 4. Alternative treatment options

	PEG-J Our study (Chapter 6)	PEG-J No data specifically on gastroparesis* (67, 68)	Direct PEJ (112, 114, 115)	Surgical Je- junostomy (113)	PRJ* No data specifically on gast- roparesis (116)
No. patients	19	20-56	2-12	26	41
Technical success rate	100%	100%	68-90%	100%	98%
Complica- tions	32% dislocation of jejunal extension	* Dislocation (27-36%) * Occlusion (3.5-35%) (67, 68)	* Volvulus (8.3%) * Jejunocolic fistula (8.3%) * Accidental withdrawal (16.6%)(115)	* 23 major in 14 patients (surgery or hospital- ization (1 death)) * 47 minor in 21 patients	10% minor (obstruction, skin infec- tion)
Effect (symptoms)	37% good 37% mod- erate	Unknown for gastroparesis	* 'Symptom improvement' in all four patients (112) * Initially 2/2, long-term 1/2 (114) * Not reported (enteral feeding tolerated in 90%) (115)	39%	Unknown for gastropa- resis
Effect (weight gain)	100%, 74% significant	Unknown	Unknown	56% weight gain	Unknown

* PRJ= Percutaneous Radiologic Jejunostomy

Figure 1. Treatment algorithm for gastroparesis
S=subjective, O=objective

Percutaneous Endoscopic Colostomy (PEC)

The final part of this thesis (**Chapter 7**) focused on another alternative application of PEG tubes: Percutaneous Endoscopic Colostomy (PEC), using the same technique as in PEG, for use in antegrade lavage in chronic constipation. We advocate for a more prominent place in daily practice for this less well known technique. Although known since 1986 (131), it is not a widely used technique. We showed safety and good short term efficacy (all patients reported a moderate (33%) or good effect (67%)). A reasonable long-term effect was seen (50%).

Remarkably, no major infections were found, which was previously considered a major problem with this technique (132, 133). This might have caused this technique to never become popular, together with the belief it is difficult to perform. However, by using a combined antibiotic regimen,

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using systemic antibiotics combined with bactericide gazes around the insertion site, as described in **Chapter 4**, no major infections have occurred. One might argue our population is young and probable in a better condition than patients getting PEC for another indication, such as volvulus, which has previously been studied. However, two studies comparing PEC for constipation and volvulus did not show any differences in the occurrence of fecal peritonitis between those two groups (132, 133).

Our analysis showed long-term success rates of 50%. Nevertheless, as shown in **Chapter 7** (Table 2), this number still compares reasonably with other, more invasive treatment options. We therefore feel that this number justifies the further exploration of this technique as a part of the therapeutic options in chronic refractory constipation.

Despite our low number of patients, our results add up to the knowledge of PEC in chronic refractory constipation. The easily applicable technique we described might contribute to a more prominent place of PEC in the current treatment of chronic constipation. In our opinion PEC, using the pull-technique known from PEG, can be applied by any gastroenterologist familiar with PEC placement. The algorithm (Figure 2) below shows subsequent steps in the treatment of chronic constipation and options for refractory complication, including positive and negative points. We point to a more prominent role of PEC placement as alternative to the Malone stoma, both prior to (definitive) colectomy.

Figure 2. Treatment algorithm for chronic constipation

** Recently, sacral neuromodulation had been approved (conditionally) for restitution from health insurance*

Future insights and research

In our opinion, PEG is the first choice in providing a long-term enteral access. In case PEG is not possible, or in certain indications such as oropharyngeal tumors or obstruction, PRG has shown to be a valuable alternative. However, complications such as dislocation of the tube remain a problem. An extensive comparison of other alternatives, such as PIG and push-PEG, would be interesting to perform in the future, in order to determine the efficacy and safety of these techniques.

Besides that, we believe that in the discussion about PEG and PRG, the clinical experience and availability will in daily practice play a major role in the shared decision making.

The importance of adequate nutrition and the risks of malnutrition should be given a more prominent position in the curriculum of every medical faculty program but specifically in the training of residents in gastroenterology. This would help to increase the awareness and, if necessary, provide enteral feeding already more early in the course of diseases. Although we noticed assiduousness of doctors leads frequently to unnecessary placement in patients with a poor prognosis (in our study: ALS patients), PEG placement should in many cases be considered more early; we observed long term use of nasogastric tubes with regular dislocation, irritation and unnecessary discomfort as well.

In the future, prospective trials may contribute to a higher level of evidence. Specifically on the 'alternative applications' such as PEG-J in the treatment of gastroparesis and PEC in chronic constipation, larger trials would add up to our results. On the use of PEG-j in gastroparesis, more studies are warranted, for we have for the first time described a sequence of patients following a stepwise approach, including the first results on Gastric Rest and PEG-J in gastroparesis.

In the future, we would suggest measuring QoL and validated symptom scores in advance of treatment and afterwards, with more thorough documentation of the effect of the treatments.

With respect to PEC, larger trials, using the same procedure and antibiotic prophylaxis as we did, would be beneficial. The diagnostic strategy should then be more clarified and similar in every patient. In our clinical experiences, no such unanimous diagnostic regimen was followed. However, we believe PEC is a minimally invasive option that should be considered in the treatment regimen, for its lower risk of major complications than surgery. More gastroenterologists (in training) should become familiar with placement of this technique during the course of training, or by courses later on.

Larger, prospective studies are warranted on most of the topics we addressed. However, the major issue with performing RCTs is that the number of patients needed would be extremely large, because of the low expected differences between procedures, as described before (e.g. antibiotic gages vs. iv. antibiotics (this would require >1000 patients per group in a non-inferiority analysis), PEG vs. PRG, botulinum toxin vs. placebo).

Overall conclusion

This thesis has provided an extended overview of PEG and its complications for many indications and various applications, and may be helpful in the decision process for daily clinical practice. The safety of prophylactic antibacterial gazes is demonstrated, as well as the safety of PEG with sedation in ALS and alternative use/indications of PEG-tubes (PEC). We aimed to create an easily applicable overview which might be useful for many clinicians and other professionals in the field of enteral feeding.

Figure 3. Algorithm for tube decision making

* NGT; nasogastric tube, NDT; nasoduodenic tube, NJT; nasojejunic tube

Gastrostomy: PEG or PRG

In conclusion, PEG is a safe procedure when careful patient and placement method is applied. It has low complication rates if placed in eligible patients. Many applications are available, which deserve more attention in current treatment algorithms of a variety of conditions. These are valuable alternatives to more invasive procedures such as surgery, due to low morbidity, high availability and the fact that they are easy to perform.

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A multidisciplinary approach with respect to patient and placement method selection as well as follow-up is an important goal to accomplish in the future. Besides that, follow-up should be standardized in order to provide continuity and a thorough registration.

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ADDENDUM

Summary in English

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9

Summary in English

This thesis has focused on Percutaneous Endoscopic Gastrostomy (PEG), describing outcomes and complications for various indications and applications. We aimed to provide a reference work for PEG. An overview of its development and history, (contra-)indications, currently available methods for placement, and alternative options, have been provided in **Chapter 1**.

A comparison of PEG with its radiologic alternative Percutaneous Radiologic Gastrostomy (PRG) was described in **Chapter 2 & 3**. A new approach to infectious complications in PEG has been described in **Chapter 4**, whereas in **Chapter 5** we described the use of sedation and complications of PEG in patients with Amyotrophic Lateral Sclerosis (ALS). Alternative applications of PEG were described in **Chapter 6 & 7**. In **Chapter 6**, the use of PEG-J (PEG with jejunal extension) in gastroparesis was described in a stepwise treatment algorithm. **Chapter 7** focused on Percutaneous Endoscopic Colostomy (PEC) in patients with refractory constipation.

In **Chapter 8**, we presented an overview of the main results, discussed new insights, and provided potential implications for clinical practice and future research.

The optimal technique for placement of a gastrostomy for long-term enteral feeding has not yet been established. Both PEG and its radiologic alternative PRG are widely used. In **Chapter 2**, we performed a systematic review and meta-analysis comparing PEG with PRG. Mortality related to the procedure and overall mortality after thirty days were reviewed, as well as infectious and tube related complications (e.g. obstruction, dislocation). Tube related complications, including dislocation, obstruction and tube defects, were higher in PRG. Procedure related and 30-day mortality, as well as infectious complications, were similar amongst groups. Specifically, subgroups including head and neck cancer (HNC) patients and motor neuron disease (MND, includes ALS) patients were studied.

Subgroup analysis in HNC patients revealed lower procedure related mortality as well as tube related complications after PEG. In MND, no subgroup differences were observed.

The studies included in the meta-analysis were relatively small (maximum of 370 patients in total). Therefore, we performed a study in the Maastricht UMC+ comparing outcomes after PEG and PRG. This study, described in **Chapter 3**, is the largest one in sample size up to now. A total of 760 procedures (469 PRG and 291 PEG) were studied, with most patients receiving gastrostomy due to dysphagia after a Cerebrovascular accident (CVA) or MND, or prophylactic in HNC (prior to radiotherapy which often causes mucositis with feeding problems).

Interestingly, a relatively high 30-day mortality occurred both in PEG and PRG (10.7% vs. 5.1%). After correcting for baseline differences, this difference between PEG and PRG was no longer significant. It was obvious that the 30-day mortality was related to the underlying illness. This means that placement of a gastrostomy should be delayed or not performed in severely ill patients with a poor condition, because the risk of severe complications and even death is too high. An alternative is nasogastric or nasojejunal tube feeding for several weeks to evaluate the course of the disease and prognosis of the patient.

In our analysis, PRG had a higher procedural success rate (97.1% vs. 91.2% in PEG). Tube related complications, responsible for numerous hospital visits (2.7% vs. 26.4% in PRG) and pain (4.1% vs. 9.4% in PRG) occurred less frequently after PEG compared to PRG.

If available and placed in carefully selected patients, PEG seems favorable over PRG due to lower complication rates. In patients with oropharyngeal tumors, stenosis, or when sedation is not possible, PRG is a valuable alternative. The choice for either PEG or PRG should be based also on local facilities and expertise.

As described in **Chapter 1**, the most common complication after PEG is peristomal wound infection. Infection rates of 40% have been reported in case no antibiotics were administered. Prophylactic intravenous (iv.) antibiotics decrease this rate to 9–15%. A new approach to prevent wound infections has been described in **Chapter 4**. This study described local antibiotic treatment with antibacterial gazes in 331 patients, without administration of iv. antibiotics. These gazes contain a bactericide ingredient (PHMB; Polyhexamethylene biguanide) and were applied immediately after PEG placement for three days. An infection rate of 9.4% occurred, which is comparable to the best results reported in literature with patients on iv. antibiotics. Advantages of the gazes compared to iv. antibiotics are its low costs (five times lower), and its practical and patient friendly use.

A specifically vulnerable group of patients was investigated in **Chapter 5**. In this chapter we described the use of sedation during PEG and its complications in patients with Amyotrophic Lateral Sclerosis (ALS). Use of sedation in ALS is controversial, and often feared due to a higher possible risk of respiratory complications in these patients, due to muscle weakness. However, no studies underlining this fear have been published yet. We analyzed 45 ALS patients from our department receiving PEG under conscious sedation (e.g. with midazolam) over a 7-year period. Lung function was mildly/moderately impaired (Forced Vital Capacity (FVC) <70%) or severely impaired (FVC <50%) in resp. 42.2% and 8.8% of patients. No respiratory complications occurred, neither during nor after

the procedure. Therefore, our data indicate that conscious sedation can be administered safely in patients with ALS, even with mild to moderate pulmonary dysfunction.

Use of a special form of PEG, namely PEG with a jejunal extension (PEG-J), in gastroparesis, was described in **Chapter 6**. A jejunal extension, attached to a regular PEG, was used when jejunal feeding is indicated. This can be the case in patients with gastroparesis. This disorder is characterized by abnormal gastric motor function with delayed gastric emptying. We described results of a stepwise treatment approach in 86 patients. First, dietary advice and prokinetics were provided. When these initial interventions failed, three months of complete nasoduodenal tube feeding with 'gastric rest' (no or minimal oral intake) was prescribed. When not successful, a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) for long term enteral feeding was placed. Results of such stepwise approach have not been described before.

A total of 50/86 patients (58%) had adequate symptom responses (good effect) to dietary advice and prokinetics. The remaining 36 patients (classified as decompensated gastroparesis) were treated with three months of gastric rest and received complete nasoduodenal tube feeding, leading to a symptom response rate of 47% (17/36). Significant weight gain was seen in all patients, independent of symptom response. In the remaining 19 symptom non-responders the enteral feeding was continued through PEG-J. Treatment was effective in 37% with respect to symptoms (7/19), with significant weight gain in all. Another 37% showed moderate symptom responses, which we did not classify as effective but seems clinically relevant. In summary, following a stepwise treatment approach in gastroparesis, an overall adequate symptom response was reached in 86% (74/86) of all patients.

Another application, namely placement of a PEG in the colon, has been described for many years (since 1986 by Ponsky et al.). However, it has not become a regularly used technique in daily practice. In **Chapter 7** we described the place of PEC in the treatment algorithm of chronic refractory constipation (e.g. not responding to diet, laxatives, and retrograde lavage). PEC is not a well-known technique, although it has been reported repeatedly since many years (since 1986). This might be due to previously reported high rates of severe infections (mostly fecal peritonitis), sometimes leading to death. We analyzed 12 patients, who all underwent PEC via a simple technique, similar to the pull technique in PEG, placed in the colon. We used the gazes described in **Chapter 4** as a supplement to iv. and oral antibiotics. In doing so, no major infections such as fecal peritonitis were seen. Other complications were all minor and easily treated, except one abscess (which lead to removal of the PEC). All patients showed an initially good or moderate effect on symptoms. At long term follow-up, some patients underwent a surgical colectomy (n=3), with PEC postponing surgery for 1-5 years. Two patients had their PEC removed due to spontaneous relief (n=2).

PEC appeared to be a safe, easy to perform procedure and an advantage is that the procedure is reversible. We postulated that PEC deserves a more prominent place in the treatment algorithm of otherwise therapy resistant chronic constipation and serves as an endoscopic alternative for surgical interventions, with reasonable long-term efficacy.

Chapter 8 we provided an overview of our main findings. In addition, a translation to daily clinical practice was made, providing easily applicable guidelines for different patient categories. Also, suggestions for further research have been provided.

Samenvatting in het Nederlands

Het onderwerp van dit proefschrift betreft Percutane Endoscopische Gastrostomie (PEG) en Percutane Radiologische Gastrostomie (PRG). Het doel was om een referentiewerk te schrijven, met de nadruk op uitkomsten en complicaties voor verschillende indicaties en toepassingen.

Een overzicht van de ontwikkeling en geschiedenis, (contra-)indicaties, beschikbare plaatsingsmethoden, en alternatieve opties, is beschreven in **Hoofdstuk 1**.

Hoofdstuk 2 en 3 beschrijven een vergelijking van PEG met het radiologische alternatief Percutane Radiologische Gastrostomie (PRG).

Een nieuwe benadering van infectieuze complicaties van PEG wordt beschreven in **Hoofdstuk 4**. **Hoofdstuk 5** beschrijft het gebruik van sedatie en complicaties van PEG bij patiënten met Amyotrofische Lateraal Sclerose (ALS).

Alternatieve toepassingen van PEG zijn beschreven in **Hoofdstuk 6 & 7**. In **Hoofdstuk 6** wordt het gebruik van PEG in een stapsgewijs behandelalgoritme beschreven bij patiënten met een maagontledingsstoornis (gastroparese). **Hoofdstuk 7** richt zich op het gebruik van Percutane Endoscopische Colostomie (PEC) bij patiënten bij refractaire constipatie.

In **Hoofdstuk 8** beschrijven we een overzicht van de belangrijkste resultaten, bediscussiëren we nieuwe inzichten, en geven we potentiële implicaties voor de klinische praktijk en toekomstig onderzoek.

De optimale techniek voor het plaatsen van een gastrostomie voor langdurig enteraal voeden is nog niet duidelijk. Zowel PEG als het radiologische alternatief PRG worden veel gebruikt. In Hoofdstuk 2 hebben we een systematische review en meta-analyse verricht waarin we PEG met PRG hebben vergeleken. De uitkomstmaten waren procedure gerelateerde mortaliteit en overall mortaliteit na dertig dagen, evenals infectieuze en sonde gerelateerde complicaties (bijvoorbeeld obstructie en/of dislocatie). Sonde gerelateerde complicaties (dislocatie, obstructie, en defecten aan de sonde) waren hoger na PRG plaatsing. Procedure gerelateerde en 30-dagen mortaliteit, evenals infectieuze complicaties, waren vergelijkbaar tussen beide groepen. We hebben specifiek naar subgroepen van patiënten gekeken, waaronder patiënten met hoofd-hals carcinoom en motor neuron ziekte (inclusief ALS). De subgroep analyse van de patiënten met hoofd-hals carcinoom toonde een lagere procedure gerelateerde mortaliteit en minder sonde gerelateerde complicaties na PEG plaatsing. Bij motor neuron ziekte patiënten werd geen verschil gezien tussen PEG en PRG.

Omdat alle studies die we meegenomen hebben in de meta-analyse relatief klein waren (maximaal 370 patiënten in totaal), hebben we de grootste studie tot op heden verricht (Hoofdstuk 3). 760 procedures werden geanalyseerd (469 PRG en 291 PEG). De meeste patiënten ontvingen een gastrostomie vanwege dysfagie na een cerebrovasculair accident (CVA) of motor neuron ziekte,

ofwel profylactisch bij hoofd-hals carcinoom (voorafgaand aan radiotherapie, waarbij vaak mucositis met voedingsproblemen ontstaat).

Een interessante bevinding was de relatief hoge 30-dagen mortaliteit bij zowel PEG als PRG plaatsingen (respectievelijk 10.7% vs. 5.1%). Na correctie voor verschillen in patiënt karakteristieken, was dit verschil niet meer significant. 30-dagen mortaliteit was gerelateerd aan de onderliggende ziekte. Dit impliceert dat het plaatsen van een gastrostomie bij ernstig zieke patiënten in een slechte conditie uitgesteld zou moeten worden, omdat het risico op ernstige complicaties en zelfs overlijden te hoog is. Een alternatief is nasogastrisch of nasojejunaal voeden gedurende enkele weken, om het beloop van de ziekte en de prognose van de patiënt te evalueren.

Het percentage succesvolle plaatsingen was hoger bij PRG in onze analyse (97.1% vs. 91.2% bij PEG). De PEG-groep had een lager aantal sonde gerelateerde complicaties, die leiden tot vele ziekenhuisbezoeken (2.7% bij PEG vs. 26.4% bij PRG) en pijn (4.1% vs. 9.4% bij PRG).

Indien beschikbaar en geplaatst in zorgvuldig geselecteerde patiënten, lijkt PEG de voorkeur te hebben boven PRG vanwege een lager aantal complicaties. Bij patiënten met orofaryngeale tumoren, stenose, of bij wie sedatie niet mogelijk is, lijkt PRG een waardevol alternatief. De keuze voor PEG of PRG zou echter eveneens gebaseerd moeten worden op lokale faciliteiten en expertise.

De meest voorkomende complicatie van een PEG, zoals beschreven in **Hoofdstuk 1**, is wondinfectie rondom het stoma (peristomaal). Zonder toediening van antibiotica worden infectie aantallen van 40% beschreven. Profylactische intraveneuze (iv) antibiotica verlagen dit naar 9-15%. In Hoofdstuk 4 wordt een nieuwe benadering in de preventie van wondinfecties beschreven. Deze studie beschrijft lokale antibiotische behandeling middels antibacteriële gazen bij 331 patiënten, zonder dat daarbij iv. antibiotica gegeven worden. Deze gazen bevatten een bactericide ingrediënt (PHMB; Polyhexamethylene biguanide), en worden direct na PEG plaatsing op de wond bij de insteekopening geplaatst, alwaar ze gedurende drie dagen blijven zitten. Er traden wond infecties op bij 9.4% van de patiënten, wat vergelijkbaar is met de beste resultaten die beschreven zijn bij het gebruik van intraveneuze antibiotica. Voordelen van de gazen vergeleken met iv. antibiotica zijn de lage kosten (de gazen zijn vijf keer goedkoper), en het praktische en patiënt vriendelijke gebruik.

Hoofdstuk 5 beschrijft het gebruik van sedatie tijdens PEG en de complicaties hiervan in een zeer kwetsbare patiëntengroep, namelijk patiënten met ALS. Het gebruik van sedatie bij deze patiënten is controversieel, en vaak gevreesd doordat er mogelijk een hoger risico op respiratoire complicaties bestaat als gevolg van spierzwakte. Echter zijn er geen studies gepubliceerd die deze angst onderschrijven.

We hebben 45 patiënten van onze afdeling geanalyseerd, die allen een PEG plaatsing ondergingen onder sedatie (met b.v. midazolam) gedurende een periode van 7 jaar. De longfunctie was mild/matig

beperkt ((Forced Vital Capacity (FVC) <70%) of ernstig beperkt (FVC <50%) bij respectievelijk 42.2% en 8.8% van de patiënten. Er traden geen respiratoir complicaties op, zowel tijdens als na de procedure. Onze data laten zien dat sedatie bij patiënten met ALS veilig toegediend zou kunnen worden, zelfs indien sprake is van een mild tot matig beperkte longfunctie.

In **Hoofdstuk 6** beschrijven we het gebruik van een bijzondere vorm van PEG, namelijk PEG met een jejunale extensie (PEG-j) bij patiënten met een gastroparese. Deze sondes worden gebruikt indien jejunale voeding geïnduceerd is. Dit kan het geval zijn bij patiënten met gastroparese, gekenmerkt door een abnormale maagmotiliteit en een vertraagde maagontlediging. Het gebruik van een stapsgewijze behandelstrategie bij 86 patiënten is beschreven in **Hoofdstuk 6**. Initieel werden dieetadviezen en prokinetica voorgeschreven aan alle patiënten. Indien deze maatregelen niet effectief bleken, werden drie maanden volledig enterale voeding via een nasoduodenale sonde, met 'gastric rest' ofwel 'maagrust' geadviseerd, waarbij geen orale inname toegestaan werd. Indien dit geen effect had op de klachten, werd een PEG-j geplaatst om langdurig enteraal te kunnen voeden. Resultaten van een soortgelijke stapsgewijze benadering zijn nooit eerder beschreven.

50/86 (58%) van de patiënten hadden een adequate symptoom respons (goed effect) op dieetmaatregelen en prokinetica. De overige 36 patiënten (geclassificeerd als gedecompenseerde gastroparese) werden behandeld met een periode van 3 maanden gastric rest, met volledige enterale sondevoeding. Dit leidde tot een symptoom respons van 47% (17/36). Alle patiënten lieten een significante toename zien van het gewicht, onafhankelijk van de symptoom respons. De overige 19 patiënten die niet respondeerden op gastric rest, kregen langdurige enterale voeding via een PEG-j. Deze behandeling leidde tot een succesvolle verbetering van de symptomen bij 37% (7/19) van de patiënten, waarbij een significante stijging van het gewicht optrad bij alle patiënten. 37% had een redelijk effect op symptomen, wat we niet als effectief hebben gescoord, maar in onze ogen wel klinisch relevant is.

Het volgen van een stapsgewijs algoritme leidt dus bij 86% van alle patiënten (74/86) tot een goed effect op de symptomen.

Als laatste beschrijven we nog een andere applicatie van PEG, namelijk plaatsing van een PEG in het colon (PEC). Deze procedure is al vele jaren geleden beschreven (sinds 1986, door Ponsky). Het is echter nooit een veelgebruikte techniek geworden in de dagelijkse praktijk.

Hoofdstuk 7 beschrijft de plaats van PEC in het behandelalgoritme van chronische refractaire constipatie (dit wil zeggen, niet responsief op dieetmaatregelen, laxantia, en retrograde spoeling/lavage). PEC is geen bekende techniek, mogelijk door het hoge aantal ernstige infecties wat in eerdere studies beschreven werd, waarbij dit meestal fecale peritonitis betrof (wat soms tot de dood kan leiden).

We beschrijven een analyse van 12 patiënten, die allen een PEC plaatsing ondergingen middels een eenvoudige techniek, gelijk aan de 'pull-techniek' gebruik bij PEG plaatsingen. De gazen die we in **Hoofdstuk 4** beschreven werden gebruikt als supplement bij iv. en orale antibiotica. Er traden geen ernstige infecties zoals fecale peritonitis op. Andere complicaties waren mild en gemakkelijk te behandelen, behoudens één abces, wat leidde tot verwijdering van de PEC. Alle patiënten hadden initieel een redelijk tot goed effect op hun klachten door het gebruik van de PEC. Op de lange termijn hebben 3 patiënten een chirurgische colectomie ondergaan, waarbij het gebruik van PEC de operatie 1-5 jaar heeft uitgesteld. 2 patiënten hebben de PEC uiteindelijk laten verwijderen omdat hun klachten spontaan verdwenen waren.

PEC lijkt veilig, is simpel te plaatsen, en is reversibel. Naar onze mening verdient PEC een meer prominente plaats in het behandelalgoritme van therapie resistente chronische constipatie, en dient PEC als een endoscopisch alternatief voor chirurgische interventies, met een redelijke lange termijn effectiviteit.

Hoofdstuk 8 toont een overzicht van onze belangrijkste resultaten en bediscussieert deze. Behoudens dat wordt er een vertaling naar de dagelijkse klinische praktijk gemaakt, waarbij gemakkelijk toepasbare adviezen voor verschillende patiënt categorieën gegeven worden. Daarnaast worden suggesties voor vervolgonderzoek gegeven.

Valorisation

Valorisation of knowledge describes the process of value creation from scientific knowledge, by making it available for economic and social utilization (1). This chapter explains the value of the obtained study results for society, including social and economic aspects, and provides possible routes of implementation in daily practice. With this thesis, we aimed to improve the knowledge about PEGs and provide an extended reference work for health care professionals, in order to improve care.

As discussed before, enteral feeding is the main indication for placement of a PEG (2). In the Netherlands, a national prevalence survey showed malnutrition was present in approximately 20% of hospitalized patients and patient in need for chronic care, taken together. Moreover, a risk of malnutrition is present in as many as 50% of patients (3). Thus, attention should always be given to a patients' nutritional status, and supplementary or complete feeding (e.g. by PEG) should be considered more often.

On the other hand, complications of PEG can be serious, sometimes even lethal (2, 4), leading to extended social and economic impact (5). With that in mind, consideration whether or not the burden of the procedure outweighs the risks, is an important item we brought to attention. Our aim was to be of help in the decision and selection process of PEG/PRG placement.

Improvement of care

This thesis focused on a topic of multidisciplinary interest and relevance. Not only gastroenterologists, but radiologists, surgeons, neurologists, otolaryngologists, general practitioners, as well as nurses are all involved in care around PEG (4, 8).

The condition of patients prior to gastrostomy has often deteriorated due to underlying disease or malnutrition itself (4, 6, 7). Therefore, complication risks should not be too easily overlooked.

As stated before, the decision to place a PEG (or not), should be careful and thorough. Our results provide evidence-based statements that can help doctors with this process. Knowledge of risk factors and possible complications for each patient group is of major importance. When implemented in daily practice, this will lead to lower morbidity and mortality.

By studying several large groups of patients, we have provided insight in a) a new, practical and cheaper way of preventing wound infections (which is a large problem of PEG); in b) the question whether PEG or PRG is best; in c) that sedation does not poses a problem in a vulnerable patient group (ALS); in d) that PEC may help to prevent colectomy in patients with refractory constipation, and in e) that PEG-J helps to improve nutritional status and provides relief symptoms in gastroparesis.

We aimed to demonstrate that these procedures can be performed on a regular basis, are relatively easy, and compare favorably over surgery due to lower invasiveness, mortality and morbidity. An important issue is the responsibility for the selection of patients: PEG or PRG. The choice is not always clear (9). This issue was addressed as early as 1985 by Booth, who warned for gastroenterologist becoming technicians instead of consultants (10). It seems that the role of technician only, is more and more common (11). We advocate for a more consulting role of the gastroenterologist, for referring doctors may not regularly see PEG patients and therefore might have difficulties with this decision.

Applicability

The results of our research deserve implementation in the clinical care. To provide a more widespread impact, we intend to use the data obtained in this thesis to write and update Dutch guidelines on PEG/PRG. Such a guideline is being developed at this moment. Incorporation of the results in this guideline ensures implementation and public availability.

This work serves an educational purpose as well, for many questions around PEG are summarized in this thesis. Such reference work about PEG was lacking. The thesis can therefore be of use by many professionals, trainees and students of multiple disciplines. Besides that, it might be the start of more prospective research.

Social

With respect to social perspectives, several improvements of current care can be achieved. Decisions about PEG placement can be ethically challenging, in particular in case patients are mentally disabled or severely ill and not able to decide for themselves. This is regularly the case in patients undergoing PEG insertion (8, 12). As a consequence, in the process around placement of a PEG, communication with the patient and the family is of the utmost importance. Moreover, significant pressure from the patient and/or family is often present, as it appears to be difficult to accept a decision to *not* place a gastrostomy (13). In that manner, our data may help in explaining the benefits and burdens or possible complications of PEG to the patient as well as the family.

Another important social aspect of PEG is the fact that the inability to eat and need for enteral feeding is likely to have a major psychosocial and emotional impact on daily life, for social events are often accompanied by or related to eating (14). Besides that, PEG tubes itself have been associated with negative feelings such as restrictions in going outside, disturbed sleep, and negative attitudes of other people towards the gastrostomy (15). Moreover, patients with PEG tubes reported to have a lower general Quality of Life (16, 17). These social aspects again emphasize the importance of careful patient selection for gastrostomy tubes.

Costs

Costs in healthcare are a topic of major interest. Every year, the total costs of health care rise, which leads to increased health care insurance costs (18). In 2016, 96 billion euro was spent on health care in the Netherlands (18). Many possible economic benefits are provided by this thesis. With respect to macro-economic levels, careful consideration of the utility of procedures and sometimes avoiding procedures can attribute to lowering costs. Moreover, lower morbidity is accompanied by lower costs, due to a lower number of hospital visits after gastrostomy and lower procedure costs in case of complications. We have shown that with PEG, these complications and regular replacement visits are much lower in number than with PRG.

The gazes we describe in Chapter 4 cost five times less than intravenous antibiotics (€0.65 per piece vs. €2.88 for iv antibiotics per use). Despite this is only a small difference in costs, in larger numbers of patients this difference becomes relevant.

Procedural costs of PEG and PRG itself are difficult to estimate and a large variation exists in literature (19-21). In our hospital prices for placement are similar, with PRG being cheaper as a procedure, but overnight stay accounting for higher costs. We have not taken replacements into account. These costs are higher in PRG. Finally, PEG and its other applications (PEG-J, PEC) are cheaper than surgery (20, 21), and enteral nutrition by PEG is cheaper than TPV (22).

We promote a stricter patient and tube selection, based on the results and findings of this thesis. This line of clinical decision making may contribute to lowering health care costs.

Conclusion

In conclusion, numerous potential benefits of the research data we have provided, are present. Various implementations have been discussed, concerning both social and economic effects.

The major benefits include optimization of patient care by personalizing tube selection, and thereby lowering mortality and morbidity. Secondly, this way of handling will contribute to lowering costs of healthcare and achieving better quality of care. The results are directly applicable and will be implemented in guidelines.

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List of publications

Published articles

D. Strijbos, D. Keszthelyi, R.M.M. Bogie, L.P.L. Gilissen, M. Lacko, J.G.J. Hoeijmakers, C. van der Leij, R. de Ridder, M.W. de Haan, A.A.M. Masclee. *A Systematic Review and Meta-Analysis on Outcomes and Complications of Percutaneous Endoscopic versus Radiologic Gastrostomy for Enteral Feeding*. J Clin Gastroenterol. 2018 Oct;52(9):753-764.

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D. Strijbos/F.G.M. Smeets, D. Keszthelyi, C.V. Hoge, J.W. Kruijmel, J.M. Conchillo and A.A.M. Masclee. *Botulinum toxin in gastroparesis: clinical efficacy and predictors of response*. Gastrointestinal Disorders

Submitted manuscripts:

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Curriculum Vitae

Denise Strijbos werd geboren op 22 September 1991 in Veldhoven. Ze groeide op in een liefdevol gezin en heeft twee jongere zussen.

In 2009 studeerde ze cum laude af van het Gymnasium, aan het Sondervick College te Veldhoven. Hierna startte ze direct met haar Geneeskunde studie in Maastricht, en behaalde haar Bachelor in 2012. Haar coschappen volgde ze in het Catharina Ziekenhuis te Eindhoven en verhuisde naar Veldhoven samen met haar partner Mike.

Het laatste jaar van de Master volgde ze bij de Maag-, Darm- en Leverziekten in het Catharina Ziekenhuis. Daar startte ze met haar onderzoek naar PEG tijdens de wetenschappelijke stage onder begeleiding van L. Gilissen. Na het behalen van haar Master in juli 2015, werkte ze gedurende 1 jaar bij de MDL in het Catharina Ziekenhuis, gecombineerd met onderzoek. In september 2016 startte ze met de opleiding tot MDL-arts, direct gevolgd door 1 jaar fulltime onderzoek, gefaciliteerd door het Catharina Ziekenhuis. Haar begeleiding tijdens dit promotietraject verliep gecombineerd, zowel vanuit het Catharina Ziekenhuis (dr. L. Gilissen, co-promotor) als het Maastricht UMC+ (professor A. Masclee, promotor, en dr. D. Keszthelyi, co-promotor), waarbij ook vanuit beide ziekenhuizen onderzoeksdata zijn verkregen.

Vanaf oktober 2017 volgt ze haar vooropleiding Interne Geneeskunde, met als opleider dr. S. Konings. Vanaf juni 2019 vervolgt ze haar opleiding gedurende 2 jaar bij de MDL in het Catharina Ziekenhuis (opleider dr. E. Schoon), gevolgd door 2 jaar in het Maastricht UMC+ (opleider prof. A. Masclee).

Abbreviations

ADM; Antroduodenal Manometry
AF; Atrial Fibrillation
ALS; Amyotrophic Lateral Sclerosis
AGA; American Gastroenterology Association
AMD; Antimicrobial Drain
ASGE; American Society for Gastrointestinal Endoscopy
BBS; Buried Bumper Syndrome
BIPAP; Bi-Level Positive Airway Pressure
BMI; Body Mass Index
BBPS; Boston Bowel Preparation Scale
BSG; British Society of Gastroenterology
CI; Confidence Interval
CIRSE; Cardiovascular and Interventional Radiological Society of Europe
COPD; Chronic Obstructive Pulmonary Disease
COX; Cyclo-oxygenase
CRP; C-Reactive Protein
CT; Computed Tomography
CVA; Cerebrovascular Accident
DARE; Database of Abstracts of Reviews of Effectiveness
DM; Diabetes Mellitus
DOAC; Direct Oral Anticoagulant
DP; Diet and prokinetics
DPEJ; Direct Percutaneous Endoscopic Jejunostomy
DTPA; Diethylenetriamine Pentaacetic Acid
EFNS; European Federation of Neurological Societies
e.g.; *exempli gratia* (for example)
EN; Enteral Nutrition
EndoFLIP; Endoscopic Functional Luminal Imaging Probe
ESPEN; European Society for Clinical Nutrition and Metabolism
FPG; Fluoroscopy Guided Gastrostomy
Fr; French
FVC; Forced Vital Capacity
HNC; Head and Neck Cancer
GR; Gastric Rest
GI; Gastrointestinal

Chapter 9

GPA; Global Physician Assessment
G-POEM/POEP; (Gastric) Per-Oral Endoscopic pyloromyotomy
HNC; Head and Neck Cancer
HRM; High-Resolution Manometry
IBD; Inflammatory Bowel Disease
IBM; International Business Machines
ICU; Intensive Care Unit
INR; International Normalized Ratio
IPPW; Isolated Pyloric Pressure Waves
IQR; Interquartile range
LMWH; Low Molecular Weight Heparin
MI; Motility index
MMS; Medical Measurement Systems
MND; Motor Neuron Disease
MRSA; Methicillin-Resistant *Staphylococcus aureus*
MS; Multiple Sclerosis
MSA; Multiple System Atrophy
MUMC; Maastricht University Medical Center
NGT; Nasogastric Tube
NJT; Nasojejunal Tube
NIPPV; Non Invasive Positive Pressure Ventilation
NOS; Newcastle Ottawa Scale
NSAIDS; Non-Steroidal Anti-Inflammatory Drugs
OGT; Oral Gastric Tube
OJT; Oral Jejunal Tube
OR; Odds Ratio
PD; Peritoneal Dialysis
PDCA; Plan Do Check Act
PEC; Percutaneous Endoscopic Colostomy
PEG; Percutaneous Endoscopic Gastrostomy
PEG-J; Percutaneous Endoscopic Gastrostomy with Jejunal extension
PEJ; Percutaneous Endoscopic Jejunostomy
PEJ; Percutaneous Endoscopic Jejunostomy
PHMB; Polyhexamethylene Biguanide
PIG; Per-oral Image Guided Gastrostomy
PLG; Percutaneous Laparoscopic Gastrostomy

PRG; Percutaneous Radiologic Gastrostomy
PRJ; Percutaneous Radiologic Jejunostomy
PRISMA; Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM; Patient Reported Outcome parameters)
PT; Prothrombin Time
PTEG; Percutaneous Transesophageal Gastro-tubing
RCT; Randomized Controlled Trial
RD; Risk Difference
RIG; Radiologically Inserted Gastrostomy
ROBINS-I; Risk of Bias in Non-randomized Studies
SD; Standard Deviation
SPSS; Statistical Package for the Social Sciences
TPN; Total Parenteral Nutrition
TSH; Thyroid Stimulating Hormone
UTVE; Ultra-thin caliber endoscope
VP; Ventriculoperitoneal
Vs; versus
Yrs; years

Dankwoord

De rollercoaster is ten einde gekomen. Eindelijk is het af. Een ongelooflijk gevoel, hoewel direct gevolgd door een zeker gevoel van gemis.

Het schrijven van dit proefschrift heeft me heel veel opgeleverd, maar zeker ook wat gekost. Ik had het niet gekund zonder jullie, al mijn lieve familie en vrienden, die me, ondanks dat ik zo weinig tijd voor jullie had, altijd onvoorwaardelijk gesteund hebben.

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Chapter 9

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