TITLE PAGE

Gastric fistula in the chest after sleeve gastrectomy: a systematic review of diagnostic and treatment options

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Abstract

This study aimed to establish the optimal diagnostic and treatment algorithm for the management of Gastric Fistula in the Chest (GFIC) after Sleeve Gastrectomy (SG) through a systematic review of published cases. A multi-database search was performed which produced 1182 results, of which twenty-six studies were included in this systematic review. The initial presentation included subphrenic collections, leaks, or (recurrent) pneumonia with associated symptoms such as persistent cough, fever and/or dyspnoea. Computed Tomography (CT) scan in combination with either Upper Gastrointestinal series (UGI) or an Esophagogastroduodenoscopy (EGD) was used to adequately diagnose the fistulas. Initial treatment was either with clips and/or clips and stents that were placed endoscopically. When unsuccessful in majority of the cases, the surgical treatment consisted in a total gastrectomy and Roux-en-Y esophagojejunostomy in a laparoscopic or open fashion.

Introduction

Sleeve gastrectomy (SG) has remained the most commonly performed bariatric procedure worldwide for over 5 years. (1) Staple line leaks are reported to occur between 1.0% and 4.3% of cases and can lead to major morbidity. (2-4) The unique physiology of sleeved stomach, is a high-pressure system from an intact pylorus distally and lower esophageal sphincter proximally, increases the risk of persistent leaks or fistulation to adjacent anatomical compartments.
Other etiologies and mechanisms include iatrogenic injuries, improper vascularization, ischemia, hematoma formation, technical problems, and staple misfiring. (2-4)
Additionally, the leak may be caused by a stenosis, kink or twisting of the sleeve. Patients with distal stenosis are more likely to have proximal leaks, because of gastric emptying impairment leading to increased intraluminal pressure and decreased compliance of the gastric tube. (5-7)

Up to 90% of gastric leaks occur at the proximal third of the staple line, typically at the gastro-oesophageal junction, leading to subphrenic abscess formation and diaphragmatic erosion in the long term. (7, 8) If not detected promptly, gastric leaks may progress to life-threatening abdominal sepsis, abscess, fistulas, and respiratory failure. Most of these complications develop acutely with the leak, but signs and symptoms may be subtle and remain undetected for some time, further increasing the risk of morbidity and mortality.
Gastric fistula in the chest (GFIC) is a rare but devastating complication of SG, comprising gastropleural and gastrobronchial fistulas. The global incidence is unknown, but reported estimates range from 0.2-0.4% of all SG cases performed. (9-11) Patients typically present with a history of gastric leak and associated symptoms of abdominal pain, fever, and malaise. However, respiratory manifestations such as a persistent cough, hemoptysis, wheeze, pleuritic chest pain, or dyspnoea are common and may be the sole presenting complaint. Diagnoses of recurrent pneumonia or pleural effusion may be made, and the underlying etiopathology of GFIC missed if not thoroughly assessed by bariatric specialists, especially given that most GFIC presents many months after primary SG. A low threshold for investigation of GFinC is therefore warranted.

Diagnosis may be established with several methods. Options for visualization include upper gastrointestinal (UGI) radiograph series with water-soluble oral contrast, computerized tomography (CT) scan, endoscopy, bronchoscopy, and intraoperative examination after methylene blue dye ingestion. However, protocols vary between institutions, and no consensus has been reached as to which method is most successful and feasible.

Treatment of GFIC focuses on isolating and draining the site of infection, optimizing nutrition, and reducing the impact upon the respiratory system. Definitive management can be extremely challenging; aggressive endoscopic sleeve dilatation and/or closure of the fistula tract may fail to control the leak, mandating highly invasive surgical intervention with both abdominal and thoracic components. Patients with GFIC are likely to be nutritionally depleted, further limiting the speed and extent of recovery. A multidisciplinary approach with stakeholders beyond the typical bariatric team may be required; thoracic surgeons, respiratory physicians, interventional radiologists, and gastroenterologists should be involved. (8) In view of the paucity of published data on GFIC, no standardized guidelines exist for the clinical evaluation, treatment timing, multidisciplinary stakeholders, and surgical strategy for GFIC. GFIC can result in long-term morbidity and be associated with high risk of mortality. Thus prompt diagnosis and effective treatment are vital.

This study aimed to establish the optimal diagnostic and treatment algorithm for the management of GFIC after SG through a systematic review of published cases.

Materials and methods

A multi-database search was conducted. The patient population of interest was all patients with a chest fistula (either a gastro-pulmonary OR gastro-bronchial OR esophageal-pleural OR gastro-pleural OR esophageal-bronchial) after sleeve gastrectomy. No specific intervention was of superior interest; all interventions were included in the current review. For outcome measures, there was particular interest in the resolution of the fistula and associated morbidity

Pubmed, Embase, Medline, and The Cochrane Library were searched from the earliest date of each database up to 18th of April 2020. The search strategy for the literature search used the following keywords and was modified for each database: [(gastro-pulmonary OR gastro-bronchial OR esophageal-pleural OR gastro-pleural OR esophageal-bronchial) AND Sleeve Gastrectomy].

Authors NS, YG, CP, and SP individually screened and selected studies on the basis of title and abstract. After primary selection, authors (NS and SP) reviewed the full text of the selected studies and determine suitability for inclusion, based on the established selection criteria. For further eligible studies, cross-references were screened. Disagreements were solved by a discussion with each other and the authors (NS, SP) until consensus was reached.

Inclusion criteria:

- Randomized controlled trial, prospective cohort study, retrospective cohort study, case (control) studies, cross-sectional studies
- Patients with a chest fistula after sleeve gastrectomy
- Chest fistulas are defined as follows: [(gastro-pulmonary OR gastro-bronchial OR esophageal-pleural OR gastro-pleural OR esophageal-bronchial) AND Sleeve Gastrectomy]
- All treatment methods were of interest
- Reported outcome measurements of interest: the resolution of the chest fistula and associated morbidity
- Literature must be available in English

In addition, to the above-mentioned search, a grey literature search was performed using Google Scholar in an attempt to reduce publication bias. This search used the same search words as

described above but modified for this database. The grey literature search resulted in no extra inclusions.

Statistical analysis

When extracted articles were in a consistent format and homogenous, a meta-analysis using the DerSimonian and Laird random effects model, (12) applying the inverse of variance as a weighing factor, which provided the pooled risk ratios (RRs) with 95% CIs. In line with the study done by El Dib et al. (13), proportional meta-analyses were done comparing the treatment of the GFIC. A meta-analysis on endoscopic and endoscopic plus surgical treatment was performed, as well as one on surgical techniques (conversion to another bariatric surgical technique or not). For each included study, data were extracted and estimated according to previously described methods. (12, 13) The I^2 was calculated to assess heterogeneity between studies. In all tests, values of $p<0.05$ were considered statistically significant. Statistical Package for Social Sciences (SPSS, Chicago, IL, USA Version 20.0) was used to prepare a database and for statistical analysis, secondly OpenMeta software was used to conduct the meta-analysis.

Results

The primary literature search produced 1182 results, including 163 duplicates. After screening for title and abstract, 46 potentially relevant studies were found and underwent a full-text critical appraisal, resulting in 20 exclusions. Reasons for exclusion were the following: seven search results were conference abstracts, seven were reviews, and six results were not available in English.

Twenty-six studies were included in this systematic review. (9, 14-39) Figure 1 summarises the search results, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (40)

Characteristics of the included studies

Among the 26 included studies, seven of them were case series, and the rest were reports describing a single case. Rebibo et al. (14) investigated 84 patients with gastric leaks (GL). Of those patients, four developed a gastro bronchial fistula, which were included in this study. (14) Campos et al. investigated gastro bronchial fistulas after both Roux-en-Y Gastric Bypass (RYGB) and SG, of which the five patients with gastro bronchial fistulas after SG were included in this review. (18) In total 55 patients were included in this review. The other characteristics can be found in table 1.

Initial presentation, diagnostics, and treatment

Table 2 gives an overview of the most frequent findings at initial presentation in patients with chest fistulas after SG. In the majority of the cases, there are subphrenic collections, leaks, or (recurrent) pneumonia with associated symptoms like a persistent cough, fever and/or dyspnoea. Figure 2 gives a graphical overview of frequencies of common symptoms and clinical findings.

Table 3 gives an overview of the diagnostic modalities and initial treatment. The majority of the included studies used a CT scan in combination with either UGI series or an

Esophagogastroduodenoscopy (EGD) to adequately diagnose the fistulas. Regarding initial treatment, most patients were treated with a combination of antibiotics, total parenteral nutrition (or enteral nutrition), and drainage of abdominal and/or thoracic collection (either with a pigtail drain or laparoscopic or open surgical drainage). Regarding treatment of the fistula itself, stents were used the most, followed by clips and sometimes surgical glue. In the study by Saliba et al. (24), multiple courses of antibiotics were needed because of recurrent pneumonia, which resolved eventually after adequate treatment of the gastro-bronchial fistula. Alghanim et al. (34) used multiple pigtail drains because of multiple chest and abdominal collections in combination with antibiotic treatment. Abraham and colleagues (32) treated their patients with a combination of total parenteral nutrition, antibiotics, and ablation of the fistula tract prior to the placement of a stent. Fuks et al. (31) had a complicated case that needed drainage of multiple collections, was treated with a stent and injection of fibrin glue, and afterward histoacryl glue. After pulmonary rehabilitation and somatostatin analogs, the patient finally recovered.

Surgical treatment

Table 4 gives an overview of all the studies that adequately described a surgical treatment approach for fistulas in the chest. Most often, there were either clips and/or clips and stents used endoscopically as the initial invasive approach. When unsuccessful, the surgical treatment consisted of total gastrectomy and Roux-en-Y esophagojejunostomy in a laparoscopic or open fashion. Also, combined thoracic and abdominal approaches were often chosen to treat the fistulas and surgically debride collections in the thorax or the abdomen. Figure 3 shows meta-analysis on endoscopic versus endoscopic and surgical treatment. We found an Odds Ratio (OR) of 0.526 (95%CI: 0.157 to 1.757, p = 0.296), suggesting no evidence to favour one approach over the other. This indicates that the majority of the patients receives endoscopic and surgical treatment. Figure 4 gives an overview of the meta-analysis done on conversion to another bariatric procedure or no conversion in the treatment of GFIC. Again no evidence was found to

support conversion to another procedure (OR 0.877 (95%CI: 0.280 to 2.751, p = 0.822)), which indicates that conversion to another bariatric surgical procedure is less performed in the treatment of GFIC.

Pre- and postoperative course

Table 5 shows the duration of the fistula and postoperative healing time. Patients had a chest fistula with a range between two days and seven years before adequate treatment. The postoperative healing time ranged from two weeks until seven years. Albanopoulos et al. (16) reported one patient that died eighteen days after the placement of a pleural drain. With the above-mentioned data in mind we have formulated a treatment algorithm for GFIC after SG. (Figure 5)

Treatment strategy after failed endoscopical treatment

Table 6 gives an overview of the occurrence of sleeve stenosis, successful endoscopic treatment and surgical strategies after failed endoscopic management. Among the 55 patients with GFIC included in this systematic review, we found 14 patients with a stenosis of the sleeve. In ten patients endoscopic treatment was succesful and in 4 of them unsuccesfull. Of these 55 patients, 22 of them GFIC were successfully managed with endoscopic therapy.

In the remaining patients in which endoscopic management was not succesfull, different surgical strategies were conducted. Thoracotomy in 14 patients, Pleural decortication in 3 patients, RYGB in 2 patients , Total Gastrectomy with Roux en Y reconstruction in 22, ReSleeve in one case, and Omega bypass above the defect in 2 patients.

Discussion

Bariatric operations have been gaining more ground over the past decade. SG is currently the most commonly used bariatric operation worldwide for the treatment of morbid obesity. However, due to the unique physiologic features of SG (increased intraluminal pressure, and intact pylorus distally, with or without distal stricture from narrowing of the incisura) leaks are inclined to become persistent and progress to chronic fistulas. (41, 42) Staple line leaks occur in up to 4.3% of cases, depending on the experience of the center, and can lead to major morbidity. (3, 31, 43, 44) Chronic gastric fistula in the chest can progress to complex anatomical situations, such as esophagogastrobronchial and/or esophagogastro-pleural fistulas. (26)

Markowitz and Herter described the first case of gastropleural fistula in 1960. (45) Historically, Gastrobronchial fistula (GBF) was first classified by Moeller and Carpenter in 1985. They classified the causes of GBF into five categories: neoplasm, prior esophageal or gastric surgeries, trauma, gastric ulcers, and subphrenic abscesses. (46) The true worldwide incidence is not known, but it is probably underreported, ranging from 0.2% up to 0.37%. (10, 11) Abdominal sepsis, abscesses, fistulas, and respiratory failure are some of the most common complications of a leak after SG. Most of these complications occur soon after the appearance of a leak. The leak may not be overt, and sepsis is not always apparent. When the fistula is finally established, the symptoms are more overt, and it becomes a life-threatening complication if left untreated. (18, 47). In case of large hiatus hernia (>2cm) visible during SG, it should be repaired. This would reduce the chance of migrating of SG in the chest. This would help prevent complications/collections occuring in the chest if leak occured. (48, 49)

This complication results from long-standing inflammation and a pus collection in the left sub-diaphragmatic space and can form several months and even over 1 year after a known leak from the staple line of a SG. Considering the increase in the number of SGs performed, the number of cases of GFIC is also likely to have increased. Most GFIC patients have been described in case reports (rather than in series). However, a GFIC usually occurs late after the procedure with

significant morbidity and mortality. (9, 47, 50) Symptoms and initial findings included: abdominal pain, fever, malaise, leukocytosis, hypoxemia, tachycardia, pulmonary symptoms, (productive cough, expectoration, hemoptysis, wheezing, pleuritic pain, left pleural effusion or lung consolidation and recurrent lung infection), peritonitis (diffuse abdominal tenderness), and intra-abdominal abscess, (localized abdominal tenderness). (47, 50) The diagnosis is established with an upper GI series with water-soluble contrast, Methylene blue dye ingestion, and CT scan. (18, 47)

In view of the lack of literature data on GFIC, there are no guidelines or consensus or standardized algorithms on the clinical evolution, timing, available resources, multidisciplinary approach, and the surgical treatment of this rare complication. (51) Several points should be taken into accounts, such as the nutritional status and general condition of the patient, the appropriateness of the previous conservative management, the local inflammatory conditions that may render the dissection challenging, and possible eventual gastro-bronchial communication.

The treatment of GFIC should be tailored to the clinical state of the patient. In the absence of major signs of sepsis, initial conservative management can be tried. (32) This observation suggests that GFIC is not a surgical emergency; it requires preoperative nutritional support to help the patient achieve an adequate nutritional status and the use of appropriate antibiotics to treat infection, thus promoting recovery from subsequent surgery. Consequently, the initial management for control of local sepsis remain as non-operative and endoscopic approaches. Treatment of GFIC is challenging and requires multiple multidisciplinary approach (radiological, endoscopic, and surgical procedures). (15)

Usually, in non-complicated patients, the management includes a non-operative treatment (interventional radiology, endoscopic and medical treatment) with encouraging results (resolution rate up to 83.4%). (52, 53) Treatment with antibiotics, nil per-os, and fluid resuscitation, attention to electrolyte balance, nutritional support, and high-dose proton pump

inhibitors is important in managing the coexistent abdominal and lung infection. Non-surgical options described in the literature include endoscopic balloon to dilate stenosis, plastic self-expandable stents, stricturotomy, or septoplasty are minimally invasive and effective techniques in resolving gastric stenosis, which is considered the leading cause of perpetuation of the fistula. (3, 41, 42, 44) Endoscopic management is always a good primary choice, which includes internal drainage, argon plasma ablation, endo-vac, and fibrin glue injection to seal the fistulous tract, clip for the closure of GFIC.

While the timing of surgical treatment is debatable, the decision to proceed surgically depends on the patient's status and the time between the primary operation and appearance of the leak. GFIC treatment can be challenging when performed by means of major abdominal and thoracic operations. Surgical management options include drainage of abscesses and collections, removal of the fistulous tract, removal of the necrotic tissue, restoration of the anatomy , laparoscopic conversion to RYGB, Roux-en-Y over the fistula, intra-thoracic/abdominal esophago/gastro-jejunal anastomosis, and total gastrectomy, segmental left lung resection, reconstruction of the diaphragm, fascial flaps from latissimus dorsi and serratus anterior. (38, 48, 54)

Limitations

Several limitations have to be mentioned. This study is a systematic review and proportional meta-analysis based on available literature. In particular, case reports and case series, since larger trials and observational cohort studies are not available. The algorithm presented in this study has been made in accordance with the evidence found, without including expert / personal opinions. Since only 55 patients were included in this study, some data may underestimate the 'real-world' burden. Good example is the mortality rate of only 1.8% in our study group. This value can either be an under- or overestimation.

Conclusion

Gastric fistula in the chest is a very rare and potentially life-threatening complication after SG. The diagnosis is often difficult to obtain and depends on a beam of clinical and radiological evidence. The treatment continues to be controversial as this complication is rarely covered in published studies with no standardized algorithm. This complication can be challenging and requires multiple multidisciplinary approaches. Treatment should be tailored to the clinical state of the patient. Continued publication of these cases is needed to enable better consensus to be reached and universal guidelines to be created for how to manage this condition.

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Figure legends:

Figure 1: PRISMA Flow chart of the selected studies for the Gastric fistula in the chest after sleeve gastrectomy

Figure 2: Overview of frequencies of common clinical findings and symptoms

Figure 3: Meta-analysis on endoscopic versus endoscopic and surgical treatment

Figure 4: Meta-analysis on conversion to another bariatric procedure or no conversion

Figure 5: Our proposed treatment algorithm for gastric fistula in the chest after sleeve gastrectomy

Abbreviations: GFIC = Gastric Fistula in the Chest, TPN = Total Parenteral Nutrition. PPI = Proton Pump Inhibitor, NPO = Nothing Per Os