MÆDICA - a Journal of Clinical Medicine

REVIEW

MAEDICA – a Journal of Clinical Medicine
2022; 17(3): 692-698
https://doi.org/10.26574/maedica.2022.17.3.692

A Review on Treatment of Perforated Peptic Ulcer by Minimally Invasive Techniques

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ABSTRACT

Peptic ulcers are caused by acid peptic damage to the mucosal layer in the gastro-duodenal area of the gut, which results in mucosal erosion that exposes the underlying tissues to the digestive action of gastro-duodenal secretions. This pathology was traditionally related to a hypersecretory acid environment, dietary factors and stress. There are other causes of ulcers such as Helicobacter pylori *infection, excessive use of NSAIDs, and smoke and alcohol abuse. Perforation and bleeding are two major complications of the disease. A typical symptom of perforated peptic ulcers (PPU) is a sudden onset of abdominal pain or acute deterioration of the ongoing abdominal pain. Perforated peptic ulcer can be diagnosed by a simple X-ray and CT scan of the abdomen. Laboratory tests are also run to rule out differential diagnosis. Although there are several choices for surgical intervention, minimally invasive techniques have been taking over as a frequent option in feasible cases. Techniques like laparoscopy have been surfacing because of their advantages. But the efficiency of minimally invasive techniques compared to conventional approach is yet to be defined. Hence, the present review of the literature aims to describe and delineate the current perspective on PPU management by minimally invasive and low risk techniques.*

Keywords: peptic ulcer, perforation, gastroduodenal, laparoscopy, hydrogels.

INTRODUCTION

Ulcers are open sores of the skin or mucus membrane characterized by sloughing of inflamed dead tissue. They are lesions on the surface of the skin or a mucous membrane characterized by a superficial loss of tissue. Ulcers most commonly occur on the skin of the lower extremities and in the gastrointestinal tract, although they may be encountered on almost any part of the body. There are many types of ulcers such as mouth ulcer, esophagus ulcer, peptic ulcer, and genital ulcer (1).

Peptic ulcer is a chronic disease that results from an imbalance between endogenous protective factors of the gastric mucosa (mucus and bicarbonate secretion, adequate blood flow, prostaglandin E2, nitric oxide, sulfhydryl compounds and antioxidant enzymes, and others) and aggressive factors (acid and pepsin secretions). Behavioural and environmental factors, including smoking, poor diet, alcohol and non-steroidal anti-inflammatory drug ingestion, and *Helicobacter pylori*

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Article received on the 2nd of June 2022 and accepted for publication on the 7th of September 2022

infection among others, have also been implicated in the etiology of gastric ulcer (2). Peptic ulcer disease (PUD) is often defined as a mucosal break greater than 3-5 mm in the stomach or duodenum with a visible depth. It is therefore an endoscopic diagnosis in contrast to dyspepsia, which is a clinical diagnosis based on symptoms alone. Peptic ulcer disease results from an imbalance between factors that protect the mucosa of the stomach and duodenum, and factors that cause damage to it. Patients with gastric and duodenal ulcers have similar presentations. They may report epigastric or retrosternal pain, early satiety, nausea, bloating, belching, or postprandial distress. These symptoms are non-specific and may be difficult to distinguish clinically from functional dyspepsia (3). Currently, different types of ulcer forms are recognized in medicine such as peptic ulcer, corneal ulcer, stomach ulcer, foot or leg ulcer, etc (4).

Peptic ulcer disease is commonly encountered, with a lifetime prevalence in the general population of 5-10% and an incidence of 0.1–0.3% *per* year (5). The increasing incidence of *Helicobacter pylori* infection, extensive use of NSAIDs, physiological stress, fasting, cocaine use, chemotherapy with bevacizumab and the increase in alcohol and smoking abuse have changed the epidemiology of this disease. Despite a sharp reduction in incidence and rates of hospital admission and mortality over the past 30 years, complications are still encountered in many patients suffering from these problems (6).

Peptic ulcer is one of the major gastrointestinal disorders worldwide which affects 10% of the world population. About 19 out of 20 peptic ulcers are duodenal. An estimated number of 15000 deaths occur each year as a consequence of peptic ulcer. Annual incidence estimates of peptic ulcer haemorrhage and perforation until 2014 were 19.4–57 and 3.8–14 *per* 100,000 individuals, respectively. The average seven-day recurrence of haemorrhage was 13.9% and the average longterm recurrence of perforation 12.2% (7).

Complications of PUD include perforation and bleeding; however, improvement in medical management has made obstruction from chronic fibrotic disease a rare event. According to different series, the prevalence of perforation in patients with PUD ranges between 2–14% (8). Perforation is a life-threatening complication of PUD, and patients with a perforated peptic ulcer (PPU) often show up with diffuse peritonitis and generalized sepsis, conditions that carry high risks for morbidity and mortality (9). The prevalence of PUD has decreased in recent decades, but this has not been followed by a similar reduction in the complications from peptic ulcers.

The reduction in PUD can be partially attributed to the onset of *H. pylori* eradication therapy and the extensive use of proton pump inhibitors. Despite the introduction of these therapies, the incidence of PPU has remained constant in many parts of the world (10), occurring in about 2–14% of peptic ulcers; it continues to be both the second most frequent cause of hollow viscous perforation requiring urgent surgery and the most frequent indication for gastric emergency surgery (11). Although there are several choices for surgical intervention, minimally invasive techniques have been taking over as a frequent option in feasible cases. Techniques like laparoscopy have been surfacing because of their advantages. But the efficiency of minimally invasive techniques compared to conventional approach is yet to be defined. With this scenario, the present review of the literature aims to describe and delineate the current perspective on PPU management by minimally invasive and low risk techniques.

CLINICAL PRESENTATION AND DIAGNOSIS

Perforated peptic ulcer often presents with non-specific abdominal symptoms which makes early diagnosis somewhat difficult. Typical symptoms include the sudden onset of severe abdominal pain, nausea and vomiting, and pyrexia. When a perforation occurs, gastric juice and air enter the peritoneal space and lead to chemical peritonitis, which leads to severe abdominal pain and tachycardia. Sudden onset of abdominal pain, tachycardia, and abdominal rigidity are the typical triad of PPU (8). Fewer than two thirds of patients present with frank peritonitis and in some cases this phenomenon may result in a delay in the diagnosis of PPU (12).

An erect chest X-ray is commonly performed in patients with acute upper abdominal pain suspected of perforation (8). However, a contrast-enhanced computed tomography (CT) is the best diagnostic modality with an accuracy of 98% (13). Furthermore, CT scans can rule out other acute abdominal conditions such as acute cholecystitis,

acute pancreatitis, acute appendicitis and acute mesenteric ischemia, etc. Some of these acute abdominal conditions may not require surgical intervention at least in the initial phase. In resource-poor healthcare facilities, an erect chest X-ray is extremely useful in detecting free air under the diaphragm confirming visceral perforation (8). Peptic ulcer perforation can also generate detectable sonographic signs such as pneumoperitoneum; free intraperitoneal air tends to accumulate around the liver, duodenum, and stomach, local thickening of the gastroduodenal wall containing an echogenic focus or line, the presence of localized extraluminal gas and fluid. However, sonography does not typically play a role in either first-line investigation or management workup of PPU (14).

Laboratory tests such as complete blood count, urea and electrolytes, C-reactive protein (CRP), serum amylase and lipase, and venous or arterial blood gases are performed in suspected PPU patients in order to rule out other diagnoses to assess the function of other systems, and lastly, to gauge the acuteness of surgical condition. For instance, elevated serum amylase and lipase levels are suggestive of acute pancreatitis (15). Similarly, white blood cell count and CRP are usually raised in most acute abdominal conditions due to inflammation or infection and they are non-specific in nature (16).

MANAGEMENT OF THE DISEASE

Drug and non-surgical management

Perforate peptic ulcer is a surgical emergency associated with high mortality if left untreated. In general, all patients with PPU require prompt resuscitation, intravenous antibiotics, analgesia, proton pump inhibitory medications, nasogastric tube, urinary catheter and surgical source control (8). Omeprazole and triple therapy for *H. pylori* eradication are useful adjuncts in the treatment of PPU. Evidence showed that omeprazole and triple therapy treatment has significantly reduced the recurrence rate. Several studies from different countries have proven that triple therapy eradication after simple closure of PPU reduced the incidence of recurrent ulcer (17). Furthermore, studies have also revealed that about 40%-80% of PPUs would seal spontaneously with conservative management, and overall morbidity and mortality were comparable (18).

Conservative management using the "Taylor method" consists of nasogastric suction, intravenous drip, antibiotics and repeated clinical assessment. A gastrografin dye study is essential to confirm the absence of leakage in patients selected for non-operative management. If patients are clinically stable and improving, especially with a sealed perforation, surgery may not be warranted. However, if they deteriorate, regardless of the presence and size of the leak, urgent operation is indicated. This suggests that PPU with a sealed perforation can be managed conservatively. The advantages of conservative management include avoidance of surgery, risks of general anaesthesia and postoperative complications. On the other hand, disadvantages include misdiagnosis and higher mortality rate if conservative management fails (19). In clinical practice, the non-operative management strategy is resource-intensive and requires a commitment of active regular clinical examination along with round the clock availability of a surgeon, and if there is clinical deterioration, emergency surgery is warranted. The essential components of PPU non-operative management can be grouped as "R"s: Radiologically undetected leak; Repeated clinical examination; Repeated blood investigations; Respiratory and renal support; Resources for monitoring; and Readiness to operate (8).

Surgical management of PPU

The feasibility of non-operative management should be weighed with the evidence that an increase in surgical delay significantly impairs surgical outcome. A cohort study stated that, over the first 24 hours after admission, each hour of surgical delay beyond hospital admission is associated with an adjusted 2.4% decreased probability of survival compared with the previous hour, over the entire observation period (20). Operative treatment is highly recommended in PPU patients with significant pneumoperitoneum or extraluminal contrast extravasation or signs of peritonitis. Performing surgery as soon as possible is recommended especially in patients with delayed presentation and those aged over 70 years (21).

There are many operative methods that could be used to treat PPU. Primary closure by interrupted sutures, closure by interrupted sutures covered with a pedicled omentum on top of the repair (Cellan-Jones repair) and plugging the perforation with a free omental plug (Graham patch) are the most commonly used techniques (8).

Vagus nerve plays an important role in the regulation of gastrin release and gastric acid secretion by stimulating parietal cells via cholinergic receptors (22). Vagal stimulation also releases histamine and gastrin from enterochromaffin like cells and G-cells, which in turn will stimulate the parietal cells to produce acid secretion. Vagotomy is a procedure that transects the vagal trunks (truncal vagotomy) or distal nerve fibers (highly selective vagotomy). Truncal vagotomy aims to reduce the gastric acid secretion, thus reducing the risks of recurrent PUD. Selective vagotomy, which spares the hepatic and celiac divisions of the vagal trunks are associated with higher long-term recurrence rates (23). Therefore, selective vagotomy is no longer performed.

Gastrectomy is a procedure of surgical removal of a part or the entire stomach. Nowadays, emergency gastrectomy is reserved for a giant ulcer or a suspicion of malignancy when it is not safe to perform omental patch repair (24). Longer operating times, ventilation and postoperative blood transfusion are associated with increased mortality (25). The larger size of perforation is associated with higher mortality and post-operative anastomotic leak (26). Gastric resections for acid reduction have become less favourable after proton pump inhibitors era and approximately up to 10% of PPU patients require gastric resection (8).

A laparotomy is a surgical procedure involving a surgical incision through the abdominal wall to gain access into the abdominal cavity for diagnosis or surgery. Laparoscopic repair techniques mirror techniques of open surgery and in particular sutureless techniques are more prominently described (27). Laparoscopic gelatin sponge plug and fibrin glue sealing can be easily performed (28). Laparoscopic approach has been frequently used as a minimally invasive technique for the treatment of PPU.

Drawbacks of surgical techniques

Surgical management has its own disadvantages in the areas concerning overall postoperative mortality, leak of the suture repair, intra-abdominal abscesses and reoperation rate. Unlike surgical techniques, low invasive techniques do not pose much postoperative complications. In turn, it helps in predetermining the postoperative period and rehabilitation. A significant advantage of minimally invasive techniques is less postoperative pain in the first 24 hours after surgery and less postoperative wound infections. Hence, these techniques are recommended in stable patients with ulcers less than 1 cm (21).

Laparoscopic approach

For the majority of its treatment history, laparotomy and the direct closure of the perforation with interrupted sutures and an omental pedicle plug (Cellan-Jones) has been the primary approach to PPU (10). However, in the last two and half decades, the minimal access approach has emerged as a viable option. Despite these solutions, not every patient is suitable for laparoscopy and thus patient selection for laparoscopic surgery is crucial (29).

The ideal surgical technique for laparoscopic repair of perforation remains undefined; laparoscopic repair techniques mirror techniques of open surgery, but it has been reported to require greater operating time. To obviate this problem, some studies of direct suture without omental patching have been published that indicate a significantly shortened duration of surgery. Avoiding omentoplasty could reduce the duration of surgeries but may be the cause of a higher rate of leakage or duodenal stricture (30). A recent study compared the efficacy of a sutureless onlay omental patch with a sutured patch after direct closure of the perforation. The operating time was significantly shorter in the sutureless onlay omental patch group. There was no statistically significant difference in the outcome between sutureless versus sutured omental patch repair. This work indicated that both techniques might be effective and safe for laparoscopic repair of PPU (31). A sutureless technique involving a gelatin sponge plug and fibrin glue sealing can also be done. However, it has not been widely adopted due to a high rate of repair site leak (32).

Peritoneal lavage is one of the key steps in the surgical treatment of PPU (27), but it can also lengthen the operating time. There is no consensus concerning the amount of fluid to be used for irrigation. The potential reasons for conversion to open surgery include the difficulty in localizing the perforation site for anatomical reasons, *i.e.*, perforation located in a region other than the duodenal anterior wall, large perforations, peritoneal adhesions from previous surgeries, and ulcers with fragile edges (33), Mannheim peritonitis index >21, and generalized peritonitis (34). A recent systematic review however confirmed a

conversion rate of only 4.9% which may suggest that (I) laparoscopic surgical training in the complex gastrointestinal surgery is becoming common place; (II) better surgical equipment and instruments may have a role to play; (III) better senior supervision in these acute surgical cases may have become more routine and lastly (IV) surgeons are gaining more experience in emergency laparoscopic techniques (35).

A PPU is related to significant postoperative morbidity and mortality regardless of whether the surgery is laparoscopic or open. The estimated postoperative mortality ranges from 1.3% to 20%, with the 30-day mortality rate reaching 20% and the 90-day mortality rate reaching up to 30% (15). Risk factors for mortality are no different for either an open or laparoscopic approach and include shock at admission, co-morbidities, resection surgery, female, elderly patients, a delay presentation of more than 24 hours, metabolic acidosis, acute renal failure, hypoalbuminemia, being underweight and smokers. The reported surgical complications after laparoscopic repair of PPU include surgical site infection (SSI), intra-abdominal collection/abscess, wound dehiscence, enterocutaneous fistulas, peritonitis, ileus, pneumonia and incisional hernias (33).

Previous studies have shown a suture leak rate of 7% with laparoscopic repair; however, more recent studies have demonstrated that this can be substantially reduced to around 2.18% (35). The best current and most up-to-date evidence suggests that there is no difference in postoperative mortality when comparing the open to the laparoscopic approach in patients with PPU. The advantages of laparoscopy in terms of postoperative pain and wound infection rate may support a minimally invasive approach as the treatment of choice where it is situationally appropriate (36).

MINIMALLY INVASIVE TECHNIQUES

Despite the economic and safety advantages, the effectiveness of laparoscopy for gastric perforations above 10 mm in diameter is limited. As a result, more materials or techniques have been developed to improve perforation sealing quality and gastric wall repair using laparoscopic surgery (37).

Hydrogels have been extensively investigated in tissue engineering and biomedicine due to their advantageous electrical, mechanical, and biological properties (38). Viscous hydrogels are in-situ gels characterized by low invasiveness, controllability, and shape adaptability, which are increasingly used for soft tissue repair in-vivo (39). However, many hydrogels lack adaptability to the gastric environment because the cross-linked chains are hydrolyzed in an acidic environment (40). The development of wet-adhesive hydrogels in an acid environment is highly demanded for gastric perforation treatment. The toughness of hydrogels is another crucial character for their applications in tissue adhesive, especially in the stomach, where they are more prone to violent deformation under physiological conditions. In the past decades, numerous tough hydrogels have been developed based on energy dissipation by breaking sacrificial bonds such as double-network hydrogels (41), nanocomposite hydrogels (42), ionically coordinated hydrogels (43), and dual-crosslinked hydrogels (44). These strategies have their own advantages and can be utilized after adjustment and specific optimization.

However, the therapeutic outcome is usually limited when the hydrogel is used for the treatment of gastric perforation due to the highly acidic gastric juice and violent deformation of the gastric wall. An ionic nano-reservoir (INR)-based dual-network hydrogel has excellent adhesion and mechanical properties; thus, it can be easily applied to the perforation site to block the perforation while promoting tissue repairing was proposed in a study. The results showed that the first network made of polyacrylamide had cross-linked on the stomach tissue within 5s under blue light, and enhanced the adhesion performance through mechanical interlock. Nano-hydroxyapatite acted as ionic INR, which can gradually release Ca^{2+} under acid environments to form the second network with sodium alginate and inhibit the swelling of hydrogel in the gastric juice. Meanwhile, adhesion was further enhanced through amide covalent bonds at the hydrogel-tissue interface with the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide/N-hydroxysuccinimide (EDC/NHS). Dual network hydrogels obtained by the INR strategy could be employed as a potential therapeutic option for gastric perforation and other similar biomedical problems (37).

Endoscopic techniques have enabled image-guided surgical manipulation of local GI tissue for minimally invasive surgery. However, insertion of endoscopes into the GI tract may cause discomfort

to the patient, and endoscopes cannot reach all parts of the small bowel. Untethered ingestible robots present a great opportunity to perform surgical interventions in all parts of the GI tract with minimal discomfort. Several robotic capsule designs were proposed for biopsy in the GI tract. One proposed wireless capsule is able to anchor itself in place by using shape memory alloy springs to push outriggers against the GI wall (45). Once aligned in place, a spiral spring is used to rotate an inner cylindrical razor against an outer cylindrical razor and cut the tissue. A magnetically controlled capsule without electronics was developed for biopsy (46). This device cuts tissue with two coaxial cylindrical magnetic razors, actuated by magnetic fields. Another capsule design, positioned in place and controlled with magnetic fields, can release and retrieve untethered microgrippers that can self-fold to grab biopsies (47). Origami-based robots have the potential to be versatile in performing *in-vivo* surgical tasks. These robots have minimal onboard electronics, and hold a cubic magnet such that they can be actuated by magnetic fields created by four external coils. Composite material origami robots can be folded up and deployed in the stomach to remove ingested button batteries and treat the remaining wounds (48). An initial robot can grab the battery through magnetic attraction, then remove it. A second robot laminated with biodegradable drug-including sheets can patch the area of inflammation. A deployable origami hydrogel patch and plug was created for gastric ulcer therapy (49). Once ingested, the origami structure can absorb water and expand up to ten times in the surface area.

Three Hall effect sensors can magnetically localize the robot, and external coils can automatically create rotating magnetic fields to guide the robot toward the ulcer location. A constant magnetic field can then be applied to place the robot on the ulcer lesion as a patch, or in the perforated ulcer as a plug. Tetherless ingestible robots have the great potential for performing minimally invasive surgery in the GI tract. Unlike endoscopic surgery, the surgical robot can access all regions of the GI tract without causing discomfort to the patient. At the region of interest, ingestible robots can remove objects, treat wounds, perform biopsies, kill pathogens, and more. However, localization and locomotion are critical limitations that stunt the feasibility of ingestible surgical robots. Precise localization and locomotion strategies are necessary in order to steer the surgical robot to the targeted area of interest (50).

CONCLUSION

Peptic ulcer disease is a common clinical concern in society, affecting people of all age groups. Perforation of peptic ulcers is one of the major complications of the disease. The laparoscopic approach is becoming an alternative to standard procedures in low risk patients. Accompaniment of perioperative modalities like the use of hydrogels can aid in a successful management of the disease. Laparoscopic techniques are recommended for stable patients with less severe conditions as the low invasiveness helps in reducing the risks and predetermining a comfortable course of the postoperative period, a high cosmetic effect, and rapid physical and social rehabilitation of patients. However, it is important to choose the most appropriate management techniques after analysing the patient's condition. The use of tetherless ingestible robots for the treatment of ulcers is also recommended as it has gained attention in the recent years. But robotics for surgery still requires further studies and evidence. ❑

Conflicts of interest: none declared.???????????
Financial support: none declared.???????????

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