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ORIGINAL ARTICLE

# Short- and long-term outcomes of surgical management of peptic ulcer complications in the era of proton pump inhibitors

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## Abstract

**Purpose** We evaluated the short-term and long-term outcomes of emergency operations for peptic ulcer (PUD) complications in a period of time in which the need for surgery is infrequent.

**Methods** Retrospective review of operated patients (2007–2015) in one medical center.

**Results** 81 patients were included (8.9 patients/year): 70 (86.4%) male; 11 (13.6%) female. Indications for operation were hemorrhage in 18 (22.2%), perforation in 62 (76.5%) and gastric-outlet obstruction in one (1.2%). Only 16 (19.8%) operations included a procedure to reduce gastric acid secretion. Six (7.4%) patients had a second operation for recurrent or persistent complication. Of these, two had a procedure to reduce gastric acid secretion in their first operation. 16 (19.8%) patients died during the index hospitalization. Three (3.7%) patients were rehospitalized for a PUD complication following 3–24 months. One patient, who had surgery for a second perforation 3 months following the first operation, was treated empirically for Helicobacter Pylori (HP) between the two operations. In comparison to perforation, patients with hemorrhage were older ($69.9 \pm 20.3$ vs. $52.1 \pm 19.9$ years; $p = 0.0015$), more commonly had a history of PUD or treatment by nonsteroidal anti-inflammotry drugs (55.6 vs. 19.4%; $p = 0.0054$), more commonly had a procedure to reduce gastric acid secretion during their index operation (61.1 vs. 6.5%; $p < 0.0001$), and had a higher mortality (38.9 vs. 14.5%; $p = 0.0406$).

**Conclusions** Mortality is high following surgery for the complications of PUD, moreso in patients undergoing surgery for hemorrhage. Reoperations and repeated hospitalizations for complications are not uncommon, even in patients who have had procedures to reduce gastric acid secretion and HP eradication.

**Keywords** Peptic ulcer · Peptic ulcer perforation · Peptic ulcer hemorrhage

## Introduction

Peptic ulcer disease (PUD) is common and may affect as many as 4% of the population at any given time [1]. Many symptomatic patients are treated medically with H2 Blockers or proton pump inhibitors (PPI) for dyspepsia without any further workup. Some are treated following diagnosis with endoscopy and/or testing for Helicobacter Pylori (HP). Improvements in both medical treatment of PUD and endoscopic treatment of complications have led to a significant decrease in the need for surgery [2]. Surgery for PUD, which was once common, is indicated today for the treatment of PUD complications not amenable to other non-surgical therapies. In this study, we evaluated the current indications for surgery and the outcome of surgery.

## Methods

We retrospectively reviewed the electronic files of patients who underwent operation for PUD in a single center between 2007 and 2015. Data collected included: demographic data (age, gender); presentation (perforation, hemorrhage, gastric outlet obstruction); previous history of known PUD and/or use of nonsteroidal anti-inflammatory drugs (NSAIDs);

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comorbidities (ischemic heart disease, diabetes, smoking, steroid use), type of operation; operative findings in the case of perforation (clear exudate, cloudy/purulent exudate or fecal exudate) and outcomes (Clavien Dindo grade III-V complications, mortality, reoperation, rehospitalization) [3, 4]. Boey Scores were calculated for patients with perforation [5]. Surgical risk for all patients was calculated according to the American College of Surgeons NSQIP Surgical Risk Calculator [6]. For the purposes of this study, reoperations for an ongoing leak following index surgery for perforation were not included. HP treatment and referral to a gastroenterologist for further workup were also noted. Differences between patients with perforation and hemorrhage, as well as risk factors for mortality, were assessed with a dedicated software program (GraphPad InStat version 3.10). Differences in average age were compared using the Mann–Whitney Test. All other categorical data were compared using the Fisher's exact test. $p < 0.05$ was considered significant. The study was approved by the local institutional review board.

## Results

Review of the electronic files identified 84 patients with ICD-9 codes suggesting they were operated for PUD complication during the study period. Three patients were excluded following review of their file, which revealed that complications were due to trauma and not to PUD. The 81 patients having surgery represent 8.9 patients operated per year, less than one a month. Patients having surgery for PUD complications accounted for approximately 0.4% of the patients operated by the surgery departments in HYMC.

70 (86.4%) of the patients were male and 11 (13.6%) were female. 18 (22.2%) had surgery for hemorrhage, 62 (76.5%) for perforation and 1 (1.2%) for gastric outlet obstruction. 18 patients operated for hemorrhage constitute 0.9% of 1922 patients hospitalized during the study period with upper gastrointestinal bleeding. 21 (25.9%) had a previous history of PUD and 13 (16.0%) were being treated by NSAIDs. In 62 patients operated for perforation, Boey's score was 0 in 35 (56.5%) patients, 1 in 11 (17.7%) patients, 2 in 12 (19.4%) patients and 3 in 4 (6.5%) patients. Peritoneal exudate was described as clear in 15 (24.2%) patients and either cloudy or purulent in 47 (75.8%) patients. In none of the patients was the exudate described as being fecal.

The types of procedures done and their frequencies are presented in Table 1. Only 18 (22.2%) had a surgical procedure to reduce gastric acid secretion. 6 (7.4%) patients were in need of repeat operation to specifically treat a recurrent or persistent PUD complication (Table 2). Five of these operations were done during the index hospitalization, the other being carried out during a subsequent hospitalization. Of these six patients, two had a surgical procedure to reduce gastric acid secretion during their first operation and one, who had a second perforation 3 months after discharge from hospital, was treated empirically for HP after the first operation. 16 (19.8%) patients died during the index hospitalization.

**Table 1** Surgical procedures done at index hospitalization

| Primary procedures | Frequency |
|---|---|
| Antrectomy | 1 |
| Antrectomy + vagotomy | 4 |
| Oversewing of bleeding ulcer | 8 |
| Gastric ulcer resection | 1 |
| Gastric ulcer suture closure of perforation | 2 |
| Omental patch | 53 |
| Vagotomy + pyloroplasty | 12 |

65 patients survived the PUD complication and were eventually discharged. Discharge recommendations varied between the patients. 25 (38.5%) patients were treated empirically for HP with amoxicillin, clarithromycin and omeprazole. All these patients were referred to a gastroenterologist for follow-up. 20 (30.8%) other patients were referred to a gastroenterologist for follow-up, and 20 (30.8) patients neither were treated empirically for HP nor recommended to follow-up with a gastroenterologist.

3 (3.7%) patients were rehospitalized for a PUD complication. Repeat hospitalization occurred following 3–24 months in these patients. One patient, who had surgery for repeat perforation 3 months following the first operation, was treated empirically for HP between the two operations. Another patient, an 85-year-old male, whose original operation for hemorrhagic shock from duodenal ulcer bleeding included oversewing of bleeding ulcer, vagotomy and pyloroplasty, bled from a gastric ulcer 2 years after the operation. This patient was being chronically treated with NSAIDs and steroids for chronic obstructive lung disease and rheumatoid arthritis. The third patient, a 78-year-old male, did not have a surgical procedure to reduce gastric acid secretion, nor was he treated empirically for HP at discharge following omental patch for duodenal ulcer perforation. He was admitted 16 months later for duodenal ulcer bleeding. Two other patients, both of whom underwent antrectomy in the initial hospitalization, were hospitalized several times with bleeding from an anastomotic ulcer. For the purposes of this study, anastomotic ulcer was not considered as either recurrent or persistent PUD.

There were 18 patients who had surgery for hemorrhage and 62 patients who had surgery for perforation. Differences between these two groups of patients are detailed in Table 3. The median number of packed red blood cell units (pRBC) infused preoperatively was 10 (range 2–19). All except one patient were operated following resuscitation of 4 or more

**Table 2** Patients in need of second operation for recurrent or persistent peptic ulcer complication

| Patients | First presentation | Surgical treatment | HP treatment | Second presentation | Surgical treatment | Perioperative mortality |
|---|---|---|---|---|---|---|
| 83 years Male | Bleeding duodenal ulcer | Oversewing of bleeding ulcer, vagotomy + pyloroplasty | No | Rebleeding from duodenal ulcer 11 days after 1st operation | Antrectomy | Yes |
| 58 years Male | Bleeding prepyloric ulcer | Oversewing of bleeding ulcer | No | Rebleeding one day after 1st operation | Oversewing of bleeding ulcer, vagotomy + pyloroplasty | No |
| 77 years Male | Bleeding gastritis | Oversewing of bleeding ulcers, vagotomy | No | Rebleeding 3 days after 1st operation | Gastrectomy | Yes |
| 73 years Female | Perforated duodenal ulcer | Omental patch | No | Massive bleeding from kissing ulcer 6 days after 1st operation | Antrectomy | Yes |
| 73 years Male | Perforated duodenal ulcer | Omental patch | Yes | Perforated gastric ulcer 3 months after 1st operation | Ulcer excision and suture closure | No |
| 38 years Male | Bleeding gastric ulcer | Oversewing of bleeding ulcer | No | Rebleeding 1 day after 1st operation | Gastrectomy | No |

**Table 3** Comparison of patients operated for hemorrhage and patients operated for perforation (one patient with gastric bowel obstruction was not included)

| | Indication for operation | | *p* value |
|---|---|---|---|
| | Hemorrhage $N=18$ | Perforation $N=62$ | |
| Age | | | |
| Mean (95% CI) | 69.9 years (59.8–80) | 52.1 (47.0–57.2) | 0.0015 |
| Age groups | | | |
| ≥ 65 years | 10 (55.6%) | 16 (26.7%) | 0.0318 |
| Risk factors | | | |
| History of PUD | 10 (55.6%) | 10 (16.1%) | 0.0015 |
| NSAID | 6 (33.3%) | 6 (9.7%) | 0.0228 |
| Either history of PUD or NSAIDs | 13 (72.2%) | 14 (22.6%) | 0.0002 |
| Heart disease | 9 (50%) | 7 (11.3) | 0.0010 |
| Diabetes | 7 (38.9%) | 12 (19.4%) | 0.1163 |
| Chronic steroids | 2 (11.1%) | 1 (1.7%) | 0.1254 |
| Active smoker | 7 (38.9%) | 9 (14.5%) | 0.0406 |
| Type of operation | | | |
| Procedure to reduce gastric acid secretion | 13 (72.2%) | 4 (6.5%) | < 0.0001 |
| Outcome | | | |
| Patients with Grade III-V complications | 10 (55.6%) | 14 (22.6) | 0.0170 |
| Mortality | 7 (38.9%) | 9 (14.5%) | 0.0406 |

*PUD* peptic ulcer disease, *NSAID* nonsteroidal anti-inflammatory drugs

pRBC. The median calculated risk for serious complications and mortality in patients operated for hemorrhage was higher compared to those with perforation (36.1 vs. 13.7%, $p<0.0001$; 6.7 vs. 0.2%, $p=0.0001$). Table 4 compares 16 patients who died to 65 patients who survived. The cause of death in 7 patients operated for hemorrhage was mainly cardiac in 3 patients, PE in one patient, and multiple organ failure secondary to shock in 3 patients. The cause of death in 9 patients who were operated for perforation was mainly cardiac in 2 patients, mainly respiratory in one patient, and multiple organ failure secondary to sepsis in 6 patients.

## Discussion

Historically, most operations were elective, and the most common operation was for intractable pain [7, 8]. Though elective operations for PUD have practically disappeared,

**Table 4** Risk factors for mortality

| | Outcome | | *p* value |
|---|---|---|---|
| | Mortality $N=16$ | Survival $N=65$ | |
| Age | | | |
| Mean (95% CI) | 76.4 years (70.1–82.6) | 51.3 (46.2–56.3) | <0.0001 |
| Age groups | | | |
| ≥65 years | 13 (81.3%) | 14 (22.2%) | <0.0001 |
| Gender | | | |
| Male | 13 (81.3%) | 57 (87.7%) | 0.4474 |
| Risk factors | | | |
| History of PUD | 4 (25%) | 17 (26.2%) | 1.000 |
| NSAID | 7 (43.8%) | 6 (9.2%) | 0.0228 |
| Either history of PUD or NSAIDs | 8 (50%) | 20 (30.8%) | 0.1575 |
| Heart disease | 9 (56.3%) | 7 (10.8%) | 0.0003 |
| Diabetes | 5 (31.3%) | 15 (23.1%) | 0.5259 |
| Chronic steroids | 2 (12.5%) | 1 (1.5%) | 0.0980 |
| Active smoker | 6 (37.5%) | 10 (15.4%) | 0.0750 |
| Presentation | | | |
| Hemorrhage | 7 (43.8%) | 11 (16.9%) | 0.0393 |
| Type of operation | | | |
| Procedure to reduce gastric acid secretion | 5 (31.3%) | 13 (20%) | 0.3324 |

*PUD* peptic ulcer disease, *NSAID* nonsteroidal anti-inflammatory drugs

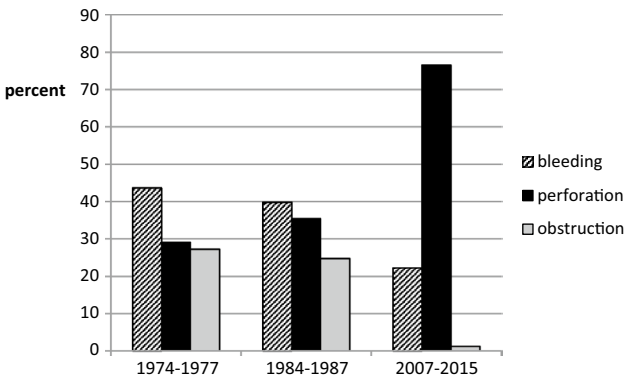


**Fig. 1** Trends in indication for operation (data on 1974–1977 and 1984–1987 from McConnell et al., data on 2007–2015 from current series)

the introduction of H2 antagonists and proton pump inhibitors (PPI) have not led to a decrease in the incidence of emergency surgery for PUD complications [8, 9]. Figure 1 compares operative trends reported by McConnell et al. at two periods (1974–1977; 1984–1987) and those reported in this study (2007–2015) [8]. The differences between our series and that of McConnell et al. are that perforation far exceeds hemorrhage as an indication for operation and that operations for gastric outlet obstruction are rarely needed. A similar change in the predominance of perforation over bleeding complication as an indication for surgery was also reported by Egberts et al. [10].

The observation that surgery for perforation now predominates over hemorrhage may have to do with advances in endoscopic treatment in arresting bleeding and the increased use of angiography, both of which have led to a decrease in the need of emergency surgery [11, 12]. Angiography has high efficacy in arresting hemorrhage and should be considered as an alternative to surgery in bleeding patients failing endoscopic therapy [13, 14]. However, this may not be the only reason for differences in indications for surgery observed between the studies. Many patients with the risk of rebleeding following primary endoscopic control of hemorrhage were once offered preventive surgery [15]. These patients are now treated non-operatively. This may also explain the lower proportion of patients having surgery for hemorrhage in our series.

Gastric outlet obstruction in need of surgery is the result of a chronic process of PUD. The relative infrequency of this indication for operation is probably related to effective medication now offered to patients with recurrent symptoms. Balloon dilatation and/or stenting is an effective alternative to surgery in patients developing obstruction with favorable long-term outcomes leading to decreased need for operation for this indication [16, 17].

PUD and its complications tend to recur. Operations to reduce gastric acid secretion, once the only effective treatment option available to avoid recurrent ulcer complications, have been largely replaced by medical treatment to reduce gastric acid secretion with or without HP eradication [18–20]. Ng et al. [21] followed 530 patients discharged after an episode of bleeding who were not treated with medication to reduce gastric acid secretion treatment after ulcer healing was confirmed by endoscopy. 169 (31.9%) patients developed a second complication (116 bleeding, 3 perforations) after a median follow-up period of 36 months. Jensen et al. [22] randomized patients to either maintenance therapy with Ranitidine or no treatment. Lower recurrent ulcer bleeding was reported for those on maintenance therapy. In another study, following an episode of major gastrointestinal hemorrhage, no major rebleeding was observed in 17 patients who were treated with ranitidine until their ulcer healed together with HP eradication compared to 4 (28.6%) of 14 patients treated with Ranitidine alone [23]. Ng et al. [24] reported on a randomized study in which HP positive patients undergoing simple closure of duodenal ulcer perforation were randomized to additional treatment following ulcer healing with either 4-week PPI treatment or 4-week PPI treatment

and HP eradication. Recurrent ulcer at 1 year was observed in 38.1% and 4.8% of the patients, respectively.

HP is found in more than 90% of patients with ulcer disease [25]. However, the incidence of HP in patients suffering from complication may be lower [26, 27]. In patients treated for PUD complication, recurrent PUD complication has been shown to diminish in patients receiving HP eradication. This is especially true in patients with PUD complicated by hemorrhage [28]. Given the low morbidity associated with antibiotic treatment aimed at HP eradication, Kauffman suggested that antibiotic treatment should be considered in nearly all patients who require operation for either acute or chronic duodenal bleeding. This approach has been shown to be true in a small series of patients [23, 29, 30]. It must be stressed, however, that patients included in these studies were included following HP testing. Kauffman suggests obtaining a biopsy from the antral mucosa during surgery to assay for urease whenever possible [28].

All these studies, many of which were done almost 2 decades ago, should serve as a reminder that PUD is a persistent disease if not treated appropriately. Empiric antibiotic treatment was started in only 38.5% of our patients and only 30.8% were referred to a gastroenterologist upon discharge. Whether active follow-up of patients is warranted should be investigated.

In this study, age, NSAID use, heart disease and hemorrhage were risk factors for mortality. A number of risk factors for increased morbidity and mortality in patients undergoing surgery for PUD complications have been described [31]. These can be grouped into three groups: patient related factors (age, chronic comorbidities); status at presentation (shock, sepsis, evidence of organ failure) and type of operation. Boey et al. [5] proposed their system of risk stratification for operation in peptic ulcer perforations based on three variables—major comorbidities, preoperative shock and long-standing perforation.

Age is a risk factor for both rebleeding and mortality in patients with upper gastrointestinal bleeding, many of whom were categorized as suffering from either PUD, erosive disease or esophagitis according to Rockall et al. [32]. In that study, the odds for mortality in increased by 2.8 in patients aged 60–79 years and by 5.04 in patients aged 80 years and above. Other studies have shown older age as a risk factor for mortality and age is one of four major risk factors that define the risk for rebleeding and death in these patients according to the Rockall risk scoring system [32–34].

Both NSAID use and heart disease were more common in patients with hemorrhage and in patients who died. The relationship of NSAIDs to ulcer disease has long been established [35]. The overall risk for ulcer complication is about 3 times greater in patients taking NSAIDs compared to non-users [36]. This risk increases with age. Gastrointestinal related mortality in NSAIDs users is also increased [36]. Overall, NSAIDs are related to an increased risk for cardiovascular events and acute renal failure [37]. Whether this is the reason for increased gastrointestinal related mortality is unclear. Though common in several series of patients suffering from PUD complications, the presence of heart disease is not listed as a distinct risk factor for PUD complication [10].

Mortality was more common in patients bleeding from their ulcer accounting for 7 (43.8%) of 16 deaths encountered in our series. The mortality rate from bleeding ulcers averaged between 6% and 10% during the era before PPI and HP eradication [11]. These numbers may be influenced by different inclusion criteria for ulcer bleeding which has diverse manifestations ranging from well-formed melena in a hemodynamically stable patient to massive hemoptysis or hematochezia in a hemodynamically unstable patient. In 5112 patients with ulcer bleeding admitted from 1990 to 1994 to the Prince of Wales Hospital in Hong Kong, emergency surgery was required in 3.5% with a surgical mortality of 12.2% [38].

Most of our patients with hemorrhage were resuscitated with significant amounts of pRBC units before they were operated. The criteria for operation in bleeding patients has long been contested. Restrictive criteria for operation may theoretically lead to a situation where a patient who ultimately requires an operation will no longer have the necessary physiological reserves to survive the procedure. If the criteria are too liberal, surgery will be carried out in many patients who could have otherwise been treated successfully non-operatively. Morris et al. [39] conducted a randomized trial that compared early to delayed surgery in patients with bleeding ulcers admitted to the General Hospital in Birmingham. Patients were stratified according to age (up to 60 years and above) and ulcer location (duodenal, gastric). The criteria for early surgery included four units of pRBC or plasma expander within 24 h, one rebleed and endoscopic stigmata. The criteria for delayed surgery included eight units of pRBC or plasma expander within 24 h, two rebleeds and persistent bleeding requiring 12 units of pRBC in 48 h or 16 units in 72 h. Patients with a history of previous bleeding were allocated to the early group. However, only a few fulfilled this criterion. All the patients included in this study were treated by endoscopy and intravenous cimetidine. A total of 57 (40%) underwent operation: 59% in the early group and 21% in the late group ($p < 0.01$). No mortality was noted in patients 60 years and younger. In patients over 60 years of age, 3 (6%) in the early group died, compared to 7 (13%) in the delayed group ($p = 0.322$). One of the patients in the early group did not have surgery within the allocated time and actually received treatment similar to the delayed group. Thus, considering the actual treatment given, mortality in the early group was 2 (4%) and in the delayed group 8 (15%) ($p = 0.098$). Though differences in mortality were

not significantly different, the authors decided to adopt different policies leading to operation in patients according to their age. Allocating patients older than 60 to a more aggressive protocol has helped decrease overall mortality to only 4% in a follow-up study [40]. Allocating different risk groups to different protocols of treatment may help achieve a balance between low mortality and the need to avoid unnecessary surgery.

The main limitation of this study is that data was retrieved from a single center. The generalizability of the data presented should be furthered assessed in other medical centers with emergency surgery services treating PUD complications. Furthermore, the retrospective nature of this study may have led to the underestimation of recurrent complications such as recurrent hospitalizations and surgery for PUD complications if these were treated elsewhere.

In conclusion, this study showed that emergency surgery for PUD complications is not infrequent despite the common use of treatment with PPI and HP eradication. However, unlike, earlier periods, surgery for acute perforation was far more common than surgery for other complications. Mortality has remained high and increases with age and NSAID use.

## Compliance with ethical standards

**Conflict of interest** Rabea Hasadia, Yael Kopelman, Oded Olsha, Ricardo Aflici and Itamar Ashkenazi declare that they have no conflict of interest.

**Research involving human participants and/or animals** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable standards. This article does not contain any studies with animals performed by any of the authors.

**Ethical approval** This study was performed following approval of the Hillel Yaffe Medical Center's institutional review board (Helsinki Committee).

**Informed consent** This was a retrospective study and formal informed consent was not required.

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