Meta-analysis of Laparoscopic Versus Open Repair of Perforated Peptic Ulcer

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ABSTRACT

Background and Objectives: Laparoscopic treatment of perforated peptic ulcer (PPU) has been introduced as an alternative procedure to open surgery. It has been postulated that the minimally invasive approach involves less operative stress and results in decreased morbidity and mortality.

Methods: We conducted a meta-analysis of randomized trials to test this hypothesis. Medline, EMBASE, and the Cochrane Central Register of Randomized Trials databases were searched, with no date or language restrictions.

Results: Our literature search identified 4 randomized trials, with a cumulative number of 289 patients, that compared the laparoscopic approach with open sutured repair of perforated ulcer. Analysis of outcomes did not favor either approach in terms of morbidity, mortality, and reoperation rate, although odds ratios seemed to consistently support the laparoscopic approach. Results did not determine the comparative efficiency and safety of laparoscopic or open approach for PPU.

Conclusion: In view of an increased interest in the laparoscopic approach, further randomized trials are considered essential to determine the relative effectiveness of laparoscopic and open repair of PPU.

Key Words: Peptic ulcer disease, Perforated peptic ulcer, Gastric ulcer, Duodenal ulcer, Laparoscopy, Meta-analysis.

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INTRODUCTION

Laparoscopic repair of perforated peptic ulcer (PPU) was first reported with the introduction of laparoscopy.[1,2] Nevertheless, the use of the procedure in routine practice has been rather limited during the 1990s, largely because of the low incidence of PPU after identification of *Helicobacter pylori* as a prime factor, and because of the effectiveness of pharmacologic treatment in eradication of the bacterium and prevention of ulcer recurrence.[3] Nevertheless, several studies have reported the use of the laparoscopic approach in clinical practice. Minimally invasive treatment of PPU involves entering the abdominal cavity after establishing a pneumoperitoneum, closure of the gastric defect, and lavage of the abdomen. Closure of the defect is facilitated either by direct suturing with or without placement of an omental patch or by introduction of biological glue with or without placement of a gelatin sponge.[4,5] The concept of sutured closure is the laparoscopic counterpart to the open technique, whereas non-sutured repair does not require laparoscopic suturing skills and has the advantage of shorter operative time.[6]

The decreasing incidence of PPU has diminished the use of the laparoscopic treatment of this condition.[7] Clinical data mostly report retrospective studies, whereas prospective trials are primarily uncontrolled,[8] thereby providing a low level of evidence. In view of experimental data demonstrating the efficacy of pneumoperitoneum compared with laparotomy in experimental models of intra-abdominal sepsis,[9] the laparoscopic approach to PPU is of considerable interest.

The present study reviews the current literature to identify the highest-quality studies and performs a comparative analysis of the clinical outcomes in laparoscopic and open sutured treatment of peptic ulcer perforation. A meta-analysis of randomized controlled trials was undertaken to examine the relative risks of morbidity and mortality for both the laparoscopic and open approaches.

MATERIALS AND METHODS

Study Protocol and Eligibility Criteria

An ad hoc study protocol was designed to address inclusion criteria and methods of analysis. Randomized controlled tri-

als providing operative outcome data of laparoscopic sutured and open sutured repair of PPU were considered for inclusion. The primary outcome measure of the present meta-analysis was the relative risk of in-hospital mortality, whereas secondary outcome measures included operative morbidity, duration of surgery, postoperative pain, and length of in-hospital stay. Data sources were searched with no language or date restrictions. Only published material was included, whereas study abstracts presented in medical congresses and indexed in peer-reviewed journals were evaluated for content.

Data Sources and Study Selection

The electronic databases of the National Library of Medicine (Medline; provider Ovid, from 1966 to July 2012), Excerpta Medica (EMBASE; provider Elsevier, from 1980 to July 2012), and the Cochrane Central Register of Controlled Trials were searched to identify relevant articles. The following search terms were used: "laparoscopy (MeSH)" AND "repair OR closure" AND "gastric OR duodenal" AND "ulcer (MeSH)." Study abstracts were reviewed and full-text articles on pertinent subjects were obtained. A second-level search included the reference lists of eligible studies and the bibliography of all relevant systematic reviews. Study eligibility was assessed independently by 2 authors in an unblinded manner. Disagreements between reviewers were resolved by consensus. The last search was run on July 14, 2012.

Data Collection and Indexing

Data were independently retrieved by the 2 reviewers upon selection of studies to include in this work. For this purpose, an electronic database was developed using Microsoft Excel (Microsoft Corp, Redmond, WA) and refined accordingly. Data items extracted from each study included author, year of publication, country of origin, period of treatment, number of participating centers, number of included patients, number of patients who received treatment, number of patients for whom operative and postoperative data were available, number of patients in each treatment arm, inclusion criteria, exclusion criteria, randomization method, blinded method (if applicable), number of patients who were evaluated after treatment, male-to-female ratio, mean age, mean American Society of Anesthesiologists score, mean Boey score, type of surgery (simple repair with or without omental patch), and mean size of perforation. Outcome measures extracted from each study included duration of surgery, conversion rate, visual analog score (VAS) at 24, 48, and 72 hours after surgery, diet toleration time, absolute number of major complications, absolute number of minor complications, and duration of in-hospital stay. Major complications

included suture line leakage, peritoneal abscess/collection, pancreatitis, fascial dehiscence, pneumonia or respiratory failure, and severe cardiac and cerebrovascular events. Wound infection or wound abscess, urinary tract infection, prolonged ileus, and incisional hernia were considered minor complications. If data were not reported, or were insufficient, the authors were contacted by e-mail, provided with information on the study, and invited to provide additional information. VAS at 48 and 72 hours after surgery were only provided by one study. A meta-analytical model for the continuous variables of duration of hospital stay and time to tolerate oral diet could not be applied because respective mean values were not provided.

Quality Assessment and Methods of Analysis

The Jadad score was calculated for each study to assess methodologic quality of the included trials. This 5-point scoring system takes a number of criteria into account, such as the randomization process, the blind assessment of investigated treatments, and reporting of dropouts.[10] A Jadad score of 1 to 2 was considered poor quality, a score of 2 to 3 was considered fair, and a score of 4 to 5 indicated good methodologic quality.

Study-specific estimates were combined using random-effects or fixed-effects models as appropriate. Weighted mean differences with 95% confidence intervals were calculated to assess the size of the effect of each type of procedure on continuous variables. Pooled odds ratios with 95% CI were calculated to measure the effect of each type of procedure on categoric variables. Heterogeneity among trials was assessed using Cochrane's Q-statistic, a null hypothesis test with a value of $P<.05$ to indicate the presence of significant heterogeneity. Publication bias was assessed using Egger regression intercept. Statistical analysis was performed using Comprehensive Meta Analysis Version 2.0 (Biostat, Englewood, NJ). Statistical expertise was provided by one of the study authors. The present meta-analysis conformed to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement standards, a methodologic protocol based on essential criteria for transparent reporting.[11]

RESULTS

Search Results and Selection of Studies

The electronic search of the databases returned 290 results (**Figure 1**). On the basis of the abstracts, 271 records were discarded because they were either confirmed retrospec-
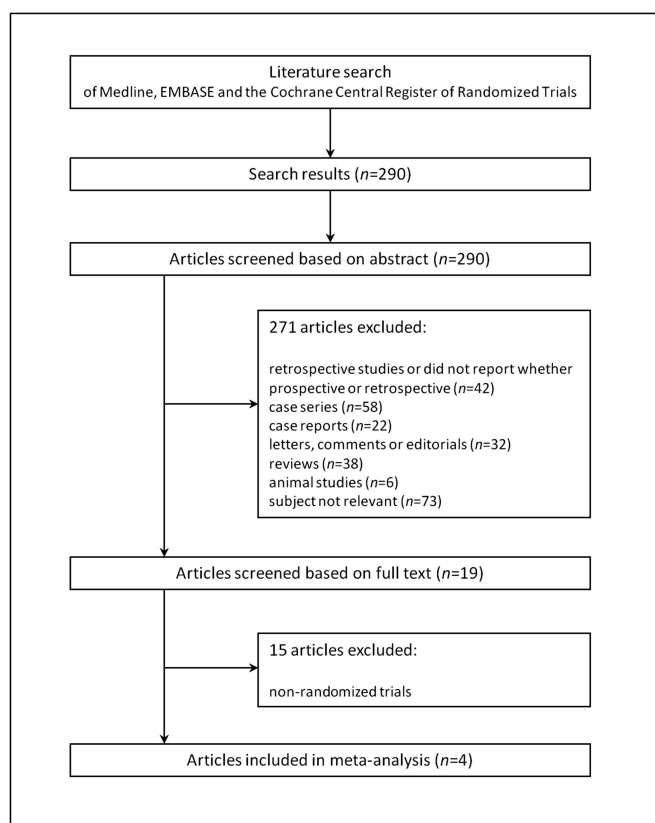
Figure 1. Flow chart of search history.

tive studies or they did not report whether they were prospective or retrospective (n=42); case series (n=58); case reports (n=22); letters, comments, or editorials (n=32); reviews (n=38); animal studies (n=6); or studies with unrelated subjects (n=73). Nineteen prospective studies with a control arm were identified and their full texts retrieved. Four randomized controlled trials fulfilling the eligibility criteria were identified and included in the meta-analysis.[12–15] Manual search of the reference lists reported in the included studies and relevant systematic reviews did not identify any further eligible studies.

Characteristics of Included Studies

Table 1 reports the characteristics of the included randomized trials. All 4 studies were randomized controlled trials published in the English language between 1996 and 2009. One was a multicentric study with 9 participating centers.[15] Three articles originated from China and one from the Netherlands, whereas 2 studies were designed by the same author team and reported on different study groups in distinct periods.[12,13] One study focused its results on biochemical evaluation of stress-associated factors rather than on clinical outcomes.[13] Nevertheless, this study was included in the analysis because it provided data on duration of surgery. Of 289 patients, 151 were included in the laparoscopic sutured repair arm and 138 in the open sutured repair arm. One study also compared the outcome of laparoscopic and open sutureless techniques, although respective data on treatments were excluded

Table 1.
Characteristics of Randomized Trials

Author	Year of Publication	Country	No. of Participating Centers	Period of Treatment	Inclusion Criteria	Exclusion Criteria	Jadad Score
Lau, et al.[12]	1996	China	1	August 1992–September 1994	Clinical diagnosis of PPU	1. Complicated ulcer 2. Bleeding ulcer 3. Prior abdominal surgery 4. Severe cardiopulmonary disease	3
Lau et al.[13]	1998	China	1	September 1995–July 1996	Age between 17 and 69 years	1. Bleeding ulcer 2. Immunosuppression	2
Siu et al.[14]	2002	China	1	January 1994–June 1997	1. Clinical diagnosis of PPU 2. Age >16 years	1. Bleeding ulcer 2. Prior abdominal surgery 3. Gastric outlet obstruction	3
Bertleff et al.[15]	2009	The Netherlands	9	March 1999–July 2005	Clinical diagnosis of PPU	1. Prior upper abdominal surgery 2. Pregnancy	3

from this analysis.[12] The main inclusion criteria entailed patients with the clinical diagnosis of PPU, whereas patients with bleeding ulcers and prior surgery in the upper abdomen were excluded by 3 studies. Male patients were predominant in the 3 studies that reported gender distribution, with an overall ratio of 1.5:1. The mean age was 54 years in the 2 studies reporting relevant data. In 3 studies, an omental patch was sutured on the repair site,[12–14] whereas in 1 study, this was not included as a routine step for both laparoscopic and open procedures.[15] Data on VAS, time to tolerate oral diet, and length of in-hospital stay could not be analyzed because several studies failed to report respective mean values or absolute numbers.

A blinded approach was not applied in any of the studies, and one study did not specify any method of randomization.[13] Hereby, 3 studies were considered to be of fair quality, with a Jadad score of 3, and 1 study was poor quality, reaching a Jadad score of only 2. All reported results adhered to the intention-to-treat concept in all studies. Data collected from patients who underwent conversion to open surgery were analyzed as data of the laparoscopic cohort.

Synthesis of Results and Outcome

Table 2 illustrates demographic data of the study populations, and Table 3 summarizes outcome measures.

Mortality

There were 3 deaths in the laparoscopic group and 8 deaths in the open group, giving rates of 2% and 6%, respectively (OR 0.36, 95% CI 0.10–1.32, P=.124). There

Table 2.
Demographic and Operative Data of the Studied Patient Populations

Author	No. of Patients (Lap/Open)	Age (Lap/Open)	Male-to-Female Ratio	ASA Score (Lap/Open)	Boey Score (Lap/Open)	Size of Perforation (mm) (Lap/Open)	Omental Patch	Conversion Rate
Lau et al.[12]	45 (24/21)	52 (52/53)	4.6:1	NR	0.27 (0.29/0.24)	NR (6 mm/5 mm)	Yes	25% (6/24)
Lau et al.[13]	22 (12/10)	NR	NR	NR	NR	NR	Yes	25% (3/12)
Siu et al.[14]	121 (63/58)	55 (54/56)	4.3:1	1.72 (1.7/1.7)	0.28 (0.24/0.33)	5.0 (5.2/4.7)	Yes	14% (9/63)
Bertleff et al.[15]	101 (52/49)	NR (66/59)*	1.5:1	NR (1.0/1.5)*	NR	NR (10.0/7.0)*	Mixed cases	8% (4/52)

NR, not reported; ASA, American Society of Anesthesiologists; lap, laparoscopic.

Numerical data are reported as mean values, unless otherwise indicated.

*Median values.

Table 3.
Summary Data of Outcome Measures

Author	Operative Time (Min) (Lap/Open)	VAS[†] (Lap/Open)	Days After Surgery to Tolerate Oral Diet (Lap/Open)	Minor Complications, (Lap/Open), n (%)	Major Complications (Lap/Open), n (%)	Reoperation, (Lap/Open), n (%)	Duration of In-Hospital Stay (d) (Lap/Open)	Mortality (Lap/Open), n (%)
Lau et al.[12]	87 (113/57)	NR (4/5)*	NR (4/4)*	2/4 (8/19)	2/1 (8/5)	0/1 (0/5)	NR (5/5)*	0/1 (0/5)
Lau et al.[13]	NR (96/35)*	NR	NR	NR	NR	NR	NR	NR
Siu et al.[14]	47 (42/52)	4.9 (3.5/6.4)	NR (4/5)*	7/14 (11/24)	3/8 (5/14)	5/1 (8/5)	NR (6/7)*	1/3 (2/5)
Bertleff et al.[15]	NR (75/50)*	(3.8/5.2)*	NR	NR	NR	NR	NR (6.5/8)*	2/4 (4/8)

n, absolute number; NR, not reported; lap, laparoscopic.

Numerical data are reported as mean values, unless otherwise indicated.

*Median values.

†24 hours after surgery.

was no evidence of between-study heterogeneity (*P*=.945) **(Figure 2)**.

Operative Time

Mean duration of surgery was 62 minutes for the laparoscopic group and 53 minutes for the open group (weighted mean difference 0.38, 95% CI 1.22–1.99, *P*=.639). There was significant evidence of between-study heterogeneity (*P*<.001) **(Figure 3)**.

Major Complications

Incidence of major complications was 6% in the laparoscopic group and 11% in the open surgery group (OR 0.47, 95% CI 0.14–1.58, *P*=.225). The level of between-study heterogeneity was low (*P*=.223) **(Figure 4)**.

Reoperation

One percent of patients of the laparoscopic group and 8% of patients of the open group underwent repeated surgery (OR 2.02, 95% CI 0.33–12.36, *P*=.446). Between-study heterogeneity was low (*P*=.151) **(Figure 5)**.

DISCUSSION

The present meta-analysis does not support favorable outcomes for minimally invasive treatment of PPU over its open surgery counterpart, as reported in the currently studied variables. Several limitations have to be taken into account to evaluate these results. Our literature search identified only 4 randomized trials. Three of these studies were of fair methodologic quality, whereas the rest failed to provide adequate data for statistical evaluation. The
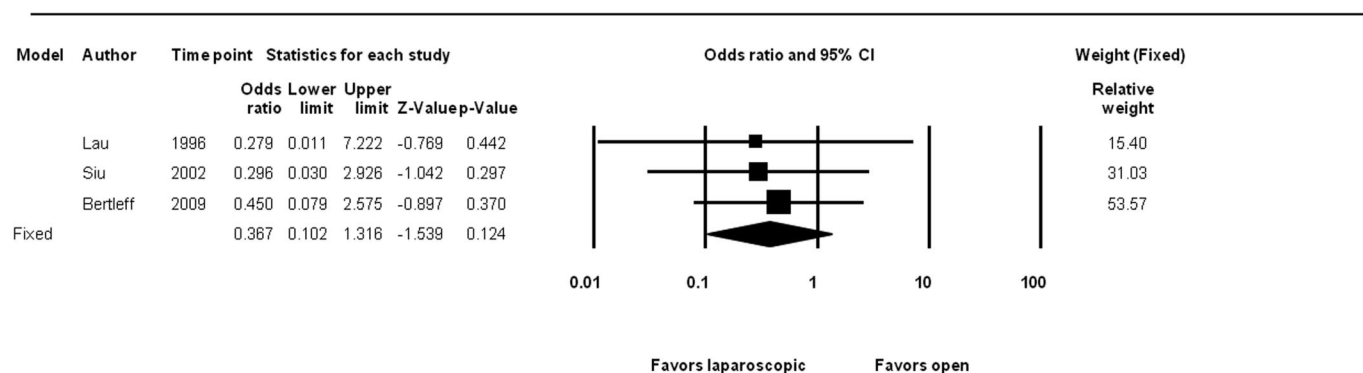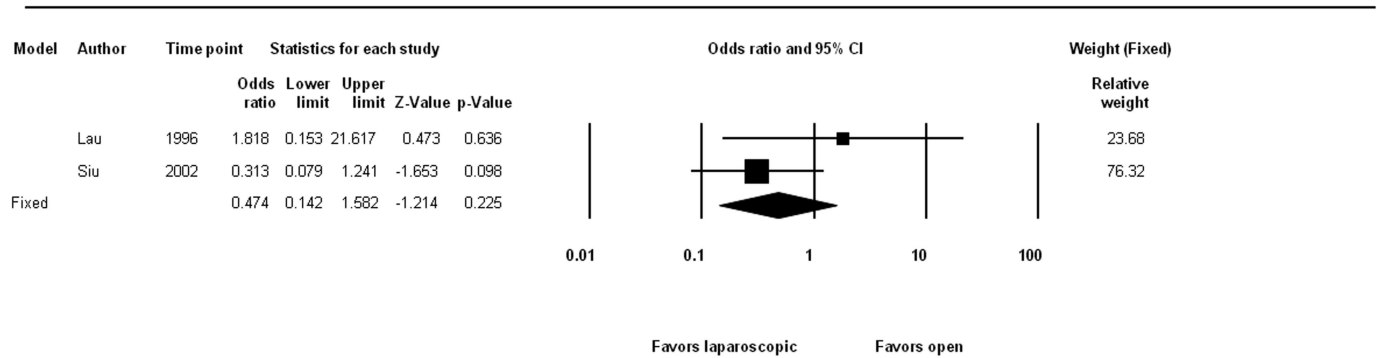

Meta Analysis

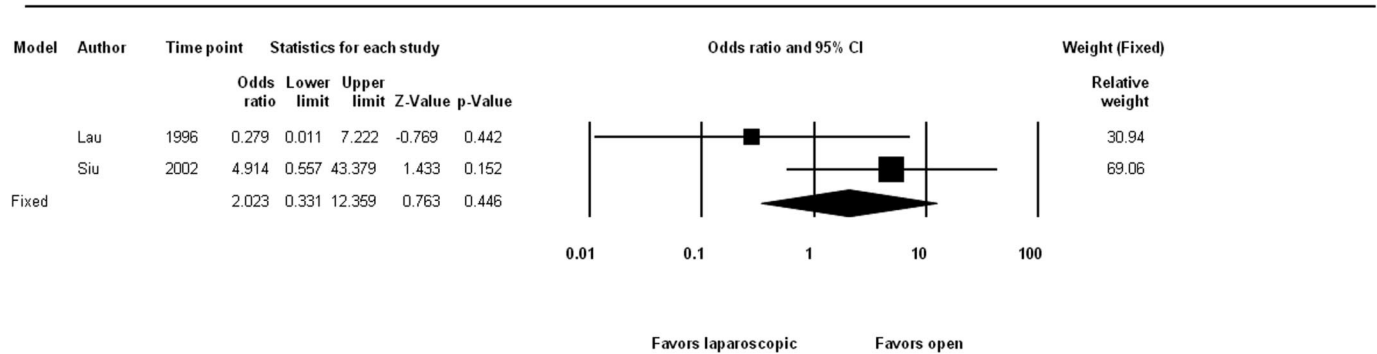**Figure 2.** Forest plot of mortality for laparoscopic and open repair of perforated ulcer.
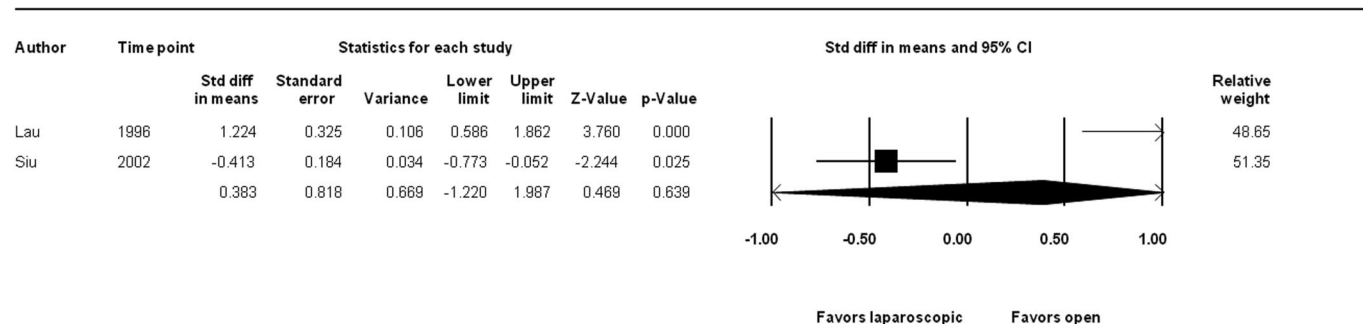
Meta Analysis

Figure 3. Forest plot of operative time for laparoscopic and open repair of perforated ulcer.

Model	Author	Time point	Statistics for each study					Odds ratio and 95% CI	Weight (Fixed)
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value		Relative weight
	Lau	1996	1.818	0.153	21.617	0.473	0.636		23.68
	Siu	2002	0.313	0.079	1.241	-1.653	0.098		76.32
Fixed			0.474	0.142	1.582	-1.214	0.225		

0.01   0.1   1   10   100

Favors laparoscopic   Favors open

Meta Analysis

Figure 4. Forest plot of major complications for laparoscopic and open repair of perforated ulcer.

Model	Author	Time point	Statistics for each study					Odds ratio and 95% CI	Weight (Fixed)
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value		Relative weight
	Lau	1996	0.279	0.011	7.222	-0.769	0.442		30.94
	Siu	2002	4.914	0.557	43.379	1.433	0.152		69.06
Fixed			2.023	0.331	12.359	0.763	0.446		

0.01   0.1   1   10   100

Favors laparoscopic   Favors open

Meta Analysis

Figure 5. Forest plot of rate of reoperation for laparoscopic and open repair of perforated ulcer.

cumulative study population was low, and the strength of the analysis was therefore limited.

The set of available data demonstrated homogeneous results for the outcome variables of mortality, complications, and reoperation rate. All studies adhered to the intention-to-treat principle, thereby rendering the outcome for laparoscopic repair more reliable. Statistical significance could not be reached for any of these variables, although odd ratios were consistently in favor of the laparoscopic repair, suggesting a potential type II statistical error. Similarly, the laparoscopic approach resulted in a lower rate of minor complications (10% vs 23%, data not shown). These results are consistent with a meta-analytical approach of nonrandomized trials, which may reflect the standard health care delivery setting.[8]

Early evidence from prospective studies demonstrated longer operating times for laparoscopic repair of PPU. Two randomized studies provided relevant data, which were contradictory, however. Longer duration of surgery was reported by Lau et al[12] in their trial conducted between 1992 and 1994, whereas a significantly reduced mean operating time was demonstrated in a more recent study by Siu et al,[14] which introduced substantial heterogeneity into the analysis. It has been suggested that acquaintance with the laparoscopic concept and laparoscopic suturing skills may result in a reduction in the duration of surgery over time.[8] A prospective analysis of more than 100 cases of laparoscopic treatment of PPU performed by surgical trainees has reported an acceptable mean operating time of 65 minutes, although most the

study population consisted of low-risk patients.[16] Peritoneal lavage is a factor of prolonged duration of surgery, although this has now been replaced with high-volume irrigation systems.[8,17]

Open repair of PPU remains the gold-standard treatment. It is simple and effective and provides long-term regression of the disease when combined with eradication of *H pylori* and recess of nonsteroidal anti-inflammatory medication.[18,19] In these patients, mortality is frequently associated with underlying sepsis and inflammatory response, which correlates with patient risk factors rather than surgical complications.[20] Considering the mitigated inflammatory reaction after elective laparoscopic procedures or laparoscopy for perforated appendicitis,[21,22] a minimally invasive approach to this emergency condition seems appealing. Outcomes of 3 randomized trials on in-hospital mortality were consistently favorable of the laparoscopic approach, although statistical significance could not be reached. The maximum relative weight was provided by the study by Bertleff et al,[15] which reported a higher peritonitis index for the laparoscopic cohort. Although there is evidence suggesting a decreased amount of operative stress in patients with peritonitis undergoing laparoscopic surgery, the true benefit of laparoscopic repair in specific patients remains to be identified. Centers with adequate experience and a community-based evaluation of laparoscopic repair of PPU have recognized old age, poor anesthesiologic status, and delayed presentation as predictive factors for mortality.[23–25] Comparative data on laparoscopic and open repair of PPU in patients stratified according to risk factors as ASA score and Boey score are still unavailable.

Systemic and procedure-related complications are a matter of concern in septic patients undergoing upper abdominal surgery. The theoretic advantage of laparoscopic treatment in terms of morbidity cannot be confirmed in the present analysis. The largest available randomized trial, which enrolled more than 100 patients, demonstrated a lower morbidity rate for the laparoscopic approach (5% vs 14%), but the data were not statistically significant.[14] This finding correlates with a cumulative evaluation of prospective and retrospective studies in 2005.[8] Because half of the studies included in this analysis were published before 2000, when laparoscopy experience was still limited, evaluation of surgery-related morbidity in the modern era of laparoscopy is a field for future investigation. Suture-site leakage is still an issue, and concerns have been raised regarding laparoscopic suturing of friable ulcer edges. An analysis of risk factors found that 84% of patients with a history of symptoms lasting longer than 9 hours developed leakage after laparoscopic
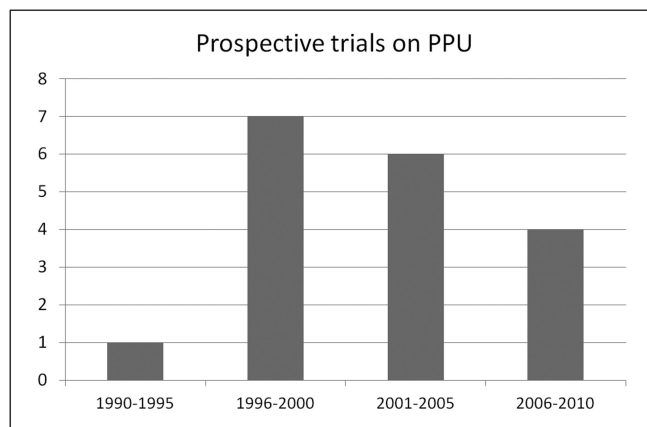

Figure 6. Absolute numbers of prospective studies on laparoscopic treatment of PPU published from 1990 to 2010.

repair.[26] Nevertheless, high-quality comparative data of laparoscopic and open repair with regard to suture failure and intra-abdominal abscess are not available.

Although the laparoscopic approach to PPU may offer significant advantages over open repair with regard to postoperative morbidity and mortality, the evidence of its efficacy is still inconclusive. A population-based study from China reported an increase in the frequency of laparoscopic repair of PPU.[27] Interestingly, our literature review has retrieved a decreasing number of published prospective trials from 1996 to date **(Figure 6)**. In view of the low incidence of ulcer perforation, interinstitutional collaboration is strongly recommended to evaluate the effect of laparoscopic repair of PPU on the setting of a randomized study.

Current evidence does not clearly demonstrate the advantages of laparoscopic versus open repair of PPU for any of the examined outcome measures. Growing interest in the laparoscopic approach may encourage the design of additional randomized trials to analyze its efficacy compared with the open approach.

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