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GASTROENTEROLOGY

Factors affecting mortality and morbidity in patients with peptic ulcer perforation

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Abstract

Background and Aim: With the introduction of H2 receptor antagonists and proton pump inhibitors, the incidence of elective surgery for peptic ulcer (PU) diseases has decreased, although complications of PU such as perforation and bleeding have remained fairly constant. The purpose of this study was to identify the risk factors that predict morbidity and mortality in patients with perforated PU.

Methods: The records of 269 patients who were operated on for perforated PU were reviewed retrospectively. The following factors were analyzed in terms of morbidity and mortality: age >65 years; gender; associated medical illness; chronic ingestion of non-steroidal anti-inflammatory drugs, aspirin, corticosteroids or immunosuppressants; alcohol ingestion and smoking habits; American Society of Anesthesiologist (ASA) status; season; delayed operation; site of ulcer perforation; and shock on admission and type of operation.

Results: There were 30 female (11.16%) and 239 male (88.84%) patients. Seventy-one (26.4%) patients had associated diseases. Simple closure was performed in 257 (95.5%) patients; 12 patients (4.5%) underwent definitive operations. A total of 108 postoperative complications were present in 65 (24.2%) patients. Twenty-three patients died (8.55%). Multivariate analysis showed that only age, ASA score, treatment delay, presence of shock and definitive operation were independent predictors of mortality. Significant risk factors that led to morbidity were ASA status, time of surgery, season, presence of shock and type of surgery. There was a significant difference concerning morbidity and mortality between simple closure of the perforation and definitive surgery.

Conclusions: Age, delayed surgery, presence of shock, ASA risk and definitive surgery are factors significantly associated with fatal outcomes in patients undergoing emergency surgery for perforated PU. Therefore, proper resuscitation from shock, improving ASA grade, decreasing delay and reserving definitive surgery for selected patients is needed to improve overall results.

Introduction

With the introduction of H2 receptor antagonists and proton pump inhibitors, the incidence of elective surgery for peptic ulcer (PU) diseases has decreased;[1–3] however, complications of PU, such as perforation and bleeding, have remained fairly constant[1,4] or increased.[2] The characteristics of perforated PU disease appear to be changing. Recently, it has been reported that there has been a relative increase in peptic ulcer perforation (PUP) in the elderly, especially in women.[3,5,6] History of using non-steroidal anti-inflammatory drugs (NSAIDs) among PU patients has increased.[7,8] Surgical treatment of perforated PU has been changing in most hospitals over recent years. With the introduction of H2 blockers and proton pump inhibitors as an effective medical treatment after surgery, simple closure has become the preferred option for many surgeons.[5,9] The rate of complications and mortality has not declined during recent decades.[6] Mortality was reported to vary between 4 and 30%[2,6,9–12] and morbidity was reported as 25–89%.[6,8,13,14] Delayed treatment, older age, presence of shock on admission, concomitant diseases and American Society of Anesthesiologist (ASA) status have been cited as the main risk factors for complication and mortality.[8–10,13,15,16] A delay of more than 24 h increased lethality seven- to eight-fold and the complication rate three-fold.[17] The main factor which could be changed to improve

prognosis of PUP is delay in diagnosis. The purpose of the present study was to identify the risk factors affecting postoperative complications and the mortality of PUP.

Methods

We reviewed the records of 269 patients operated on for perforated PU at the Emergency Surgery Department of the Ankara Numune Training and Research Hospital, between January 2001 and January 2004. Patients with perforated malignant tumors or marginal ulcers were excluded.

The diagnosis of perforation was based on clinical features, blood tests, routine laboratory tests and radiological findings (i.e. plain abdominal X-ray) and confirmed intraoperatively in all cases. Clinical factors in relation to morbidity and mortality were investigated using univariate and multivariate analyses. The following factors were analyzed: age; gender; previous ulcer history; associated medical diseases; chronic ingestion of NSAIDs, aspirin, corticosteroids or immunosuppressants; alcohol ingestion and smoking habits; season; ASA status; delayed operation; type of ulcer perforation; presence of shock on admission; and type of operation. The time between presumed perforation and surgery was considered as delayed if it was more than 24 h. All incidences of death within 30 days of operation were accepted as operative mortality.

Ulcer type was analyzed according to four different types. Type I ulcers are located on the lesser curvature at, or proximal to, the incisura; type II ulcers are located both on duodenal and prepyloric areas; type III ulcers are located within 2 cm of the pylorus; and type IV ulcers are located in the proximal stomach or in the gastric cardia.

Surgical approach was performed as a non-definitive operation (simple closure) or as a definitive operation. Simple closure included a Graham patch closure alone or closure combined with an omental patch. Definitive operation included the techniques of vagotomy + antrectomy, vagotomy + pyloroplasty and subtotal gastrectomy + gastroenterostomy.

Statistical analysis

Data analysis was performed using SPSS for Windows (version 10.0, Chicago, IL, USA). The χ^2 test or Fisher's exact test (where appropriate) were used to assess the significance of differences in categorical data. Statistically significant variables assessed by univariate analyses were entered into a multivariate logistic regression analyses to determine independent factors that are predictive of mortality and morbidity. Differences were considered significant when $P < 0.05$.

Results

Of the 269 patients, 239 (88.8%) were male and 30 (11.2%) were female, with a male to female ratio of 8:1. The disease was most common in the second and third decades; the overall mean age was 43.41 ± 18.66 years (range 16-87 years). Mean age of females was 51.83 ± 22.05 years (range 17-87 years), while the mean age of males was 42.31 ± 17.96 years (range 16-82 years) ($P = 0.04$). Clinical features of patients with perforated PU are shown in Table 1. PUP was mainly present in younger male patients (mainly in second and third decades) and in older female patients (mainly in fourth and sixth decades). Seventy-one patients (26.4%) had associated diseases which are listed in Table 2. Sixty-nine percent of patients ($n = 185$) had free air under the diaphragm according to a chest X-ray. A simple closure was performed in 95.5% of patients ($n = 257$), while 12 patients (4.5%) underwent a definitive operation. As a definitive procedure, four patients had simple closure + truncal vagotomy + gastroenterostomy; six patients had simple closure + truncal vagotomy + pyloroplasty; one patient had simple closure + truncal vagotomy + antrectomy, and one patient had subtotal gastrectomy + gastroenterostomy. The choice of surgical procedure depended on several factors; gastric resections were performed only if the ulcers were too large for simple closure, the patients with gastric or duodenal ulcers with severe scarring that cause stenosis or obstruction were operated on with simple closure + bypass procedure. Two patients had a history of operation for PUP and therefore the vagatomy + bypass procedure was performed on these patients. A total 108 postoperative complications were seen in 65 (24.2%) patients (Table 3). Pneumonia and wound infection were the most frequent postoperative complications. A total of 23 patients died (8.5%). The most frequent causes of death were myocardial failure ($n = 9$, 39.1%) and sepsis ($n = 8$, 37.8%) (Table 4).

The results of univariate analyses of clinical variables in relation to mortality are presented in Table 1. A stepwise logistic regression analysis showed that older age, ASA status, delayed admission to hospital, presence of shock, and the type of operation were independent predictors of mortality (Table 5). With every increase in ASA status, risk of mortality increased 4.5 times. Definitive operation increased mortality risk 16.5 times and admission of patients with presence of shock increased mortality 7 times. Patients older than 65 years had 6.4 times higher mortality risk than younger patients. Admission to hospital later than 24 h also increased mortality risk.

Univariate analysis demonstrated that age, associated medical diseases, season, time of surgery, presence of shock, ASA status, perforation size and type of surgery were related to morbidity (Table 1). However, multivariate analysis identified ASA status, time of surgery, season, presence of shock and type of surgery as independent predictors of morbidity. Each increase in ASA status caused an increase in the morbidity risk by 2 times. Patients that were admitted after 24 h had a 3.4 times higher morbidity risk than patients admitted before 24 h (Table 6). In winter, morbidity of patients increased. Time of admission to hospital was the same in every season. However, patients admitted to hospital in winter were older than patients admitted in other seasons. Therefore, this factor might be the reason behind the high morbidity seen in winter.

Discussion

During the past few decades the incidence of perforations has declined in the young age groups and among men, but has risen among elderly people.[6,18–20] In our study, PUP was still common in younger patients. Smoking among young people is common in Turkey, which may explain our higher incidence of perforation in young males. Male patients had PUP frequently at younger ages, while female patients had PUP most commonly in the fourth to sixth decades. In fact, an absolute increase has been reported in

Table 1 Clinical characteristics of patients in terms of morbidity and mortality

Variable		N	%	Morbidity (+)	%	*P*-value	Mortality (+)	%	*P*-value
Sex	Male	239	88.8	54	22.6	0.090	15	6.3	<0.001
	Female	30	11.2	11	36.7		8	26.7	
Age (years)	<65	216	80.3	35	16.2	<0.001	3	1.4	<0.001
	>65	53	19.7	30	56.6		20	37.7	
Drug use	Present	24	8.9	4	16.7	0.369	0	0	0.117
(NSAID + steroid)	Absent	245	91.1	61	24.9		23	9.4	
Smoking	Present	197	73.2	47	23.9	0.846	11	5.6	0.004
	Absent	72	26.8	18	25.0		12	16.7	
Alcohol use	Present	33	12.3	10	30.3	0.379	2	6.1	0.585
	Absent	236	87.7	55	23.3		21	8.9	
Associated illness	Present	71	26.4	29	40.8	<0.001	17	23.9	<0.001
	Absent	198	73.6	36	18.2		6	3.0	
Season	Spring	66	24.5	8	12.1	<0.001	3	4.5	<0.001
	Summer	62	23.0	10	16.1		1	1.6	
	Autumn	67	24.9	17	25.4		3	4.5	
	Winter	74	27.5	30	40.5		16	21.6	
Time of surgery	<24 h	189	70.3	30	15.9	<0.001	7	3.7	<0.001
	>24 h	80	29.7	35	43.8		16	20.0	
Shock	Present	16	5.9	15	93.8	<0.001	11	68.8	<0.001
	Absent	253	94.1	50	19.8		12	4.7	
ASA score	ASA I	14	5.2	3	21.4	<0.001	0	0	<0.001
	ASA II	157	58.4	18	11.5		1	0.6	
	ASA III	59	21.9	18	30.5		4	6.8	
	ASA IV	32	11.9	20	62.5		12	37.5	
	ASA V	7	2.6	6	85.7		6	85.7	
Perforation type	Type I	7	2.6	2	28.6	0.214	1	14.3	0.019
	Type II	—	—	—	—		—	—	
	Type III	242	90.0	55	22.7		17	7.0	
	Type IV	20	7.4	8	40.0		5	25.0	
Perforation size	<0.5 cm	191	71.0	30	15.7	<0.001	3	1.6	<0.001
	0.5–1 cm	59	21.9	23	39.0		12	20.3	
	>1 cm	19	7.1	12	63.2		8	42.1	
Surgical procedure	Non-definitive	257	95.5	58	22.6	0.005	18	7.0	<0.001
	Definitive	12	4.5	7	58.3		5	41.7	

ASA, American Society of Anesthesiologist; NSAID, non-steroidal anti-inflammatory drugs.

Table 2 Associated medical illnesses of patients

Illness	No. (%)
Cardiovascular disease	34 (38.2)
Pulmonary disease	19 (21.3)
Diabetes mellitus	15 (16.9)
Renal failure	4 (4.5)
Hepatic disease	3 (3.4)
Malignancy	3 (3.4)
Other	11 (12.3)

Table 3 Postoperative complications of patients

Complication	No. (%)
Respiratory failure	40 (37.04)
Wound infections	20 (18.52)
Paralytic ileus	10 (9.25)
Renal failure	10 (9.25)
Sepsis	9 (8.34)
Cardiac failure	8 (7.41)
Anastomotic dehiscence	6 (5.55)
Cerebral vascular disease	2 (1.86)
Intra-abdominal abscess	2 (1.86)
Gastrointestinal bleeding	1 (0.92)

elderly women in different studies.[5,6,21] We found that female sex was associated with a higher mortality rate than males. The higher mortality rate among women might be due to the older age of women than men. The mortality rate among the elderly patients undergoing surgery for perforated PU is as high as 12–47%.[15,21–24] In this study, patients older than 65 years had a higher mortality rate when compared to younger patients (37.7% *vs* 1.4%). Associated medical diseases and diagnostic delay may account for the higher morbidity and mortality rates in the elderly patients in our study.

Risk of postoperative death and complications are closely related to the duration of perforation.[6,8,10,11,15,17,21] Thirty percent of patients were admitted to our surgical department with a perforated ulcer that had been present for more than 24 h. Elderly patients were commonly admitted to the hospital more than 24 h after the perforation had occurred. A delay of more than 24 h increased lethality 6.5 times and the complication rate 3.4 times in our study. Most of our patients came from rural areas and they were referred to us from smaller hospitals. The present study is in agreement with previous ones and reveals the importance of early surgical intervention to improve survival rates.[3,15,17,22]

The incidence of NSAID use (9%) was low in the present study. The reason for this low percentage in comparison with other studies may be due to the low mean age of our patients. Strong association between ulcer perforation and smoking was reported in several studies.[25,26] Smoking is a causal factor for ulcer perforation.[25] The risk was increased by a factor of 10 in smokers among both men and women. Smoking prevalence of 84% and 86% have been reported among patients with duodenal ulcer perforations,[27,28] and smokers have a three-fold higher mortality rate from PU than non-smokers.[29] However, smokers had a lower mortality rate in this study because most elderly patients who had higher mortality were non-smokers.

Duodenal and pyloric ulcers show seasonal variations. More perforation occurred in early summer (May, June, July) and early winter (November, December).[6,30] Several studies[31,32] show increased perforation rates in early summer and decreased rates during late summer. In our study, incidence of PUP was the same in all seasons. Sonnenberg *et al*. confirmed that the highest mortality was seen in January and the lowest mortality was seen in July.[33] Although the mortality rate was higher in winter in this study, the ratio of elderly patients with late admission was higher in winter. In addition, the 81% of patients with preshock were admitted to the hospital in winter and therefore season was not an independent predictor of mortality.

ASA scores served as valuable predictors of mortality in the management of perforated PU. High ASA score (ASA III; IV) increased the mortality.[13,16] Each increase in ASA score increased morbidity 2 times and mortality 4.5 times in our patients.

The choice of surgical procedure in emergency is still debated. Even though simple closure has proved to be safe, some authors have suggested that definitive surgery decreases the recurrence rate without increasing the operative morbidity and mortality.[34–36] However, some studies show no difference in mortality between the non-definitive and definitive procedure.[15,37–40] Most surgeons choose simple closure instead of a definitive procedure due to higher risk in patients with perforated PU. The mortality and morbidity rates of gastric resection were also significantly increased in elderly patients with perforated gastric ulcers, as shown in our study.[41] Simple closure is an adequate surgical treatment for PUP in the elderly.[5,14,21] Boey *et al*. found a mortality rate of 7.8% in 2558 PUP patients with simple closure.[34] The discovery of the role of *Helicobacter pylori* in PU and successful treatment against *H. pylori* provides the choice of simple closure combined with treatment against *H. pylori*.[9,11,42] Open or laparoscopic primary suture of perforated peptic ulcer is increasingly advocated as the optimal surgical treatment in recent years.[11,43–45] Gastric resection is usually reserved for giant ulcers when it is not safe to perform a simple closure alone.[40] With non-definitive surgery, we also avoided the late consequences of vagotomy or gastrectomy. We preferred the simple closure in most of our patients. Although higher risk patients were also treated with simple closure,

Table 4 Causes of mortality

Cause	No. (%)
Myocardial infarct + cardiac arrhythmia	9 (39.10)
Pneumonia + ARDS	4 (17.39)
Septicemia + intra-abdominal abscess	8 (37.78)
Renal failure	1 (4.3)

ARDS, Acute Respiratory Distress Syndrome.

Table 5 Stepwise logistic regression analysis results affecting mortality of patients

	B	Sig.	Exp (B)	95% CI for EXP (B)	
				Lower	Upper
ASA score	1.506	0.003	4.510	1.683	12.086
Delayed admission	1.880	0.011	6.551	1.545	27.783
Age (>65 years)	1.864	0.021	6.449	1.327	31.341
Presence of shock	1.953	0.027	7.052	1.255	39.614
Surgical procedure (definitive surgery)	2.807	0.003	16.556	2.659	103.083

ASA, American Society of Anesthesiologist; CI, confidence interval.

Table 6 Stepwise logistic regression analysis results affecting morbidity of patients

	B	Sig.	Exp (B)	95% CI for EXP (B)	
				Lower	Upper
ASA score	0.716	0.001	2.047	1.352	3.099
Delayed admission	1.225	0.001	3.403	1.698	6.821
Season (winter)	0.806	0.036	2.239	1.056	4.751
Presence of shock	2.537	0.024	12.644	1.407	113.594
Surgical procedure (definitive surgery)	1.223	0.085	3.398	0.844	13.671

ASA, American Society of Anesthesiologist; CI, confidence interval.

mortality and morbidity rates of patients who had undergone simple closure were lower than patients who had definitive procedures.

The mortality and morbidity of PU disease have not decreased after the introduction of H2 receptor antagonists and despite many advances in pre- and postoperative care.[2,6] During the past few decades, patients have become older and had more coexisting medical diseases and use of NSAIDs has increased. Mortality rates varied between 4 and 30% in different studies.[2,6,9–12] Our mortality rate was 8.6% ($n = 23$) and morbidity rate was 24.2% ($n = 65$), with respiratory failure and wound infections being the most common cause of morbidity. We believe that such low mortality rates in our series could be explained by the low mean age of the patients which were treated with the preferred simple closure.

In conclusion, we defined the risk factors for morbidity and mortality of PUP. Increased ASA scores, delay of more than 24 h, presence of shock, and definitive surgery increased the morbidity and mortality of PUP. We found that simple closure is safe with few side-effects and should be combined with treatment against *H. pylori* and should be chosen instead of an acid reducing operation. In order to improve prognosis of patients with PUP, diagnosis and treatment should not be delayed and the associated medical diseases should be treated. Elderly patients have obscure clinical symptoms, often leading to an initial wrong diagnosis. Therefore, the possibility of PUP in elderly patients with abdominal pain should be kept in mind.

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