Original article

Surgical delay is a critical determinant of survival in perforated peptic ulcer

D. L. Buck[1], M. Vester-Andersen[2] and M. H. Møller[3] on behalf of the Danish Clinical Register of Emergency Surgery

Departments of Anaesthesiology and Intensive Care Medicine, [1]Copenhagen University Hospital Hvidovre, Hvidovre, and [2]Copenhagen University Hospital Herlev, Herlev, and [3]Department of Intensive Care, 4131, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

Correspondence to: Dr M. H. Møller, Department of Intensive Care, 4131, Copenhagen University Hospital Rigshospitalet, Blegdamsvej 9, DK – 2100 Copenhagen, Denmark (e-mail: mortenhylander@gmail.com)

Background: **Morbidity and mortality following perforated peptic ulcer (PPU) remain substantial. Surgical delay is a well established negative prognostic factor, but evidence derives from studies with a high risk of bias. The aim of the present nationwide cohort study was to evaluate the adjusted effect of hourly surgical delay on survival after PPU.**

Methods: **This was a cohort study including all Danish patients treated surgically for PPU between 1 February 2003 and 31 August 2009. Medically treated patients and those with a malignant ulcer were excluded. The associations between surgical delay and 30-day survival are presented as crude and adjusted relative risks (RRs) with 95 per cent confidence intervals (c.i.).**

Results: **A total of 2668 patients were included. Their median age was 70·9 (range 16·2–104·2) years and 55·4 per cent (1478 of 2668) were female. Some 67·5 per cent of the patients (1800 of 2668) had at least one of six co-morbid diseases and 45·6 per cent had an American Society of Anesthesiologists fitness grade of III or more. A total of 708 patients (26·5 per cent) died within 30 days of surgery. Every hour of delay from admission to surgery was associated with an adjusted 2·4 per cent decreased probability of survival compared with the previous hour (adjusted RR 1·024, 95 per cent c.i. 1·011 to 1·037).**

Conclusion: **Limiting surgical delay in patients with PPU seems of paramount importance.**

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Introduction

Perforated peptic ulcer (PPU) is a complication of peptic ulcer disease in which gas and gastroduodenal fluid leak into the peritoneal cavity. The incidence has been estimated at six to seven per 100 000 inhabitants[1,2]. Mortality rates as high as 25–30 per cent have been reported[3–6]. Sepsis is known to be a frequent and leading cause of death in patients with PPU; an estimated 30–35 per cent of patients have sepsis on arrival at the operating theatre[7] and sepsis is believed to account for 40–50 per cent of fatalities[7–9]. Within 30 days of surgery more than 25 per cent of patients develop septic shock[10], which carries a mortality rate of 50–60 per cent[11,12].

One of the cornerstones in the treatment of sepsis is intravenous broad-spectrum antibiotic therapy, administered within the first hour of diagnosis[11]. Kumar and colleagues[13] reported a significant association between each hour of delay in the start of antimicrobial treatment and in-hospital mortality. Another keystone in the treatment of sepsis is source control, which in PPU is synonymous with surgery[11]. Surgical delay in PPU is a well established negative prognostic factor[14]. However, the evidence derives from studies with a high risk of bias[15], and no study has assessed the association between hourly surgical delay and adverse outcome[14].

The aim of the present nationwide cohort study was to evaluate the risk of surgical delay by hour and adverse outcome in patients with PPU.

Methods

This nationwide cohort study with prospective data collection was approved by the Danish Data Protection Agency, and did not require informed patient consent according to Danish law. The manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[16].

Study population

All patients who had surgery for benign gastric or duodenal PPU in all 35 hospitals caring for patients with PPU in Denmark between 1 February 2003 and 31 August 2009 were included. Medically treated patients and those with a malignant ulcer were not included. There was no age restriction.

Danish Clinical Register of Emergency Surgery

Patients with PPU were identified using computerized data from the Danish Clinical Register of Emergency Surgery (DCRES)[1]. The DCRES was founded in 2003 by the Danish public healthcare authorities. The aim was to monitor the quality of care provided to patients with complicated peptic ulcer disease by Danish public hospitals, through the registration of quality standards, indicators and prognostic factors. Reporting to the database is mandatory for all Danish hospitals. Because emergency services are provided solely by the public healthcare system, all patients treated surgically for PPU in Denmark are included. The DCRES database includes baseline characteristics as well as information about the preoperative, intraoperative and postoperative phases of care.

Data extraction and management

The following baseline and clinical data were registered: age; sex; presence of shock (systolic blood pressure less than 100 mmHg and heart rate exceeding 100 beats/min); coexisting diseases; haemoglobin and creatinine levels on admission; use of aspirin, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, steroids and anticoagulants; alcohol abuse; daily use of tobacco; American Society of Anesthesiologists (ASA) fitness grade; and surgical delay.

The primary data were recorded by the surgeon using a standard case report form. The information was subsequently validated and transferred to an electronic database by the local DCRES representative at each site. The exact date of death was ascertained through linkage of the patient's civil registration number with the Danish Civil Registration System[17].

Outcome measure

The primary outcome measure was survival within 30 days of the index surgical procedure.

Statistical analysis

Baseline and clinical characteristics are presented as distribution frequencies among all patients with PPU in Denmark from 2003 to 2009. Logistic regression modelling was used to examine survival within 30 days of surgery as a function of time from admission to surgery (surgical delay) using 1-h intervals. Results are presented as crude and adjusted relative risks (RRs) with 95 per cent confidence intervals (c.i.). Adjustment was made for the following well established prognostic dichotomous co-variables: age over 65 years, shock at admission, co-morbidity and ASA grade III–V[14]. Baseline and clinical characteristics were missing for fewer than 5 per cent of the patients. The prevalence and pattern of missing values in the patient cohort were evaluated, and the data were found not to be missing completely at random. Consequently, multiple imputation for the missing values was performed[18,19]. The regression models of the imputed data set were validated using goodness-of-fit tests and model diagnostics, and showed no indication of lack of fit. Two-sided $P < 0{\cdot}050$ was considered statistically significant. Data were analysed using SPSS® version 20.0 (IBM, Armonk, New York, USA).

With a binary response variable, five co-variables, $\beta = 0{\cdot}80$, $\alpha = 0{\cdot}05$ and an anticipated small effect size, it was calculated that 643 patients were required to detect an association between the variables and the endpoint[20,21].

Results

A total of 2668 patients who had surgery for gastric or duodenal PPU were included. Their median age was 70·9 (range 16·2–104·2) years and 55·4 per cent (1478 of 2668) were female. Some 67·5 per cent (1800 of 2668) had at least one of six co-morbid diseases (*Table 1*) and 45·6 per cent (1217 of 2668) had an ASA fitness grade of at least III. Alcohol abuse was present in 18·9 per cent of the patients (504 of 2668) and 61·3 per cent (1635 of 2668) smoked daily (*Table 1*). A total of 708 patients (26·5 per cent) died within 30 days of surgery.

Over the first 24 h after admission, each hour of surgical delay beyond hospital admission was associated with a median decrease in 30-day survival of 2·0 (range 0·8–9·9) per cent. The survival rate was 95·7 per cent when surgery was initiated within 1 h of hospital admission, 88·9 per cent when initiated within 2 h, 81·8 per cent when started within 3 h, decreasing to 50·0 per cent after a surgical delay of 7 h (*Fig. 1*). The 30-day survival rate was 20 per cent when the surgical delay was more than 24 h. The median delay before surgery was 5 (interquartile range 3–12) h; at that point the 30-day survival rate was 64·2 per cent.

Only 2·7 per cent of all patients were treated surgically within the first hour of hospital admission (*Fig. 1*). Some 18·3 per cent underwent surgery within 3 h of admission and 50·6 per cent by 6 h. Even 12 h after admission, more

Table 1 Baseline and clinical characteristics among 2668 patients with peptic ulcer perforation in Denmark, 1 February 2003 to 31 August 2009

	No. of patients ($n = 2668$)
Age > 65 years	1665 (62·4)
Female sex	1478 (55·4)
Malignant disease or AIDS	187 (7·0)
Chronic obstructive pulmonary disease	392 (14·7)
Diabetes	193 (7·2)
Heart disease	901 (33·8)
Liver cirrhosis	141 (5·3)
Chronic disease	783 (29·3)
ASA fitness grade	
I	563 (21·1)
II	888 (33·3)
III	857 (32·1)
IV	323 (12·1)
V	37 (1·4)
Use of anticoagulants	133 (5·0)
Use of aspirin	766 (28·7)
Use of steroids	347 (13·0)
Use of NSAIDs	1094 (41·0)
Alcohol abuse*	504 (18·9)
Daily smoker	1635 (61·3)
Shock on admission†	430 (16·1)
Serum haemoglobin < 6·0 mmol/l	277 (10·4)
Serum creatinine > 130 μmol/l	688 (25·8)

*More than 36 g alcohol per day (men) or more than 24 g alcohol per day (women). †Blood pressure below 100 mmHg and heart rate over 100 beats per min. AIDS, acquired immunedeficiency syndrome; ASA, American Society of Anesthesiologists; NSAID, non-steroidal anti-inflammatory drug.

than a quarter of the patients had not been treated in the operating theatre.

When surgical delay was assessed as a continuous variable, the crude RR of death was 1·035 (95 per cent c.i. 1·024 to 1·047). After adjusting for known adverse prognostic variables, the RR was 1·024 (1·011 to 1·037); that is, every hour of surgical delay was associated with an adjusted 2·4 per cent decreased probability of survival compared with the previous hour over the entire observation period. Surgical delay accounted for 12·8 per cent of the variance in 30-day survival (R^2).

Discussion

In this nationwide cohort study of 2668 patients treated surgically for PPU, every hour of surgical delay was associated with a 2·4 per cent decreased probability of surviving 30 days. Furthermore, a substantial number of patients had delayed surgery.

The strengths of the present study include its size, the nationwide population-based design, the complete follow-up for ascertainment of survival, and the adjustment for known potential confounders. Data collected during routine clinical work may be inaccurate and incomplete; however, participation in the DCRES is mandatory in Denmark, and extensive efforts are made to ensure the validity of the data[22]. Some patient records had missing data for prognostic characteristics. Multiple imputation was done to control for possible bias; this is the optimal way of handling missing data[18,19]. Time to start of effective antimicrobial treatment, an important prognostic predictor of adverse outcome, is not registered in the DCRES database. Other significant possible confounding by unmeasured factors cannot be excluded. Follow-up for more than 30 days would also have been desirable in this patient population as there may have been deaths due to surgery after this time[23]. Finally, the importance of delay in initial presentation to hospital has not been addressed in the present study.

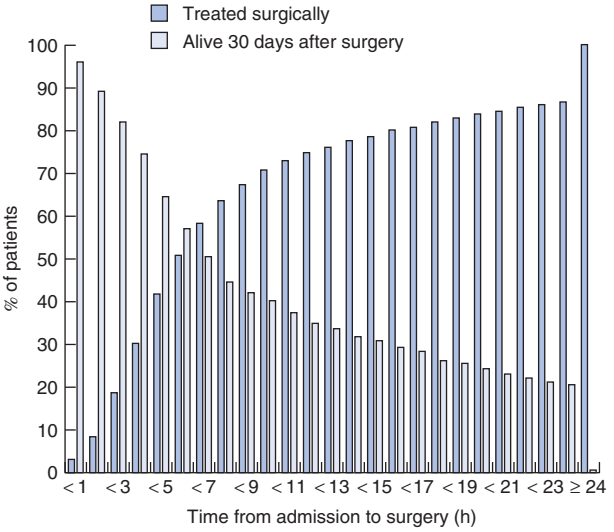

Fig. 1 Cumulative percentage of patients treated surgically and percentage alive 30 days after surgery in relation to time after hospital admission

Delayed operation is recognized as a contributor to adverse outcome in many areas of emergency surgery[24]. The primary cause in general surgery seems to be diagnostic delay[24]. Reasons behind delayed surgery for PPU are sparsely explored, but seem to be associated with out-of-hospital perforation, lack of peritoneal signs, late attendance by the surgeon, attendance by a non-senior surgeon and lack of pulse oximetry[25]. Patients with out-of-hospital perforation are often unselected and it may take time to reach the diagnosis[24]. Those with atypical symptoms are often not prioritized, compared with patients with signs of an abdominal emergency. Previous studies have reported the strong negative prognostic impact of delayed surgery for PPU[14]. However, the evidence

derives primarily from studies using unadjusted analyses, and with few patients[14], risking bias[15], and no study has assessed surgical delay as a continuous variable. A possible reason for the strong association between delay and adverse outcome could be the increased risk of developing severe sepsis. Longstanding perforation is associated with peritoneal contamination, positive peritoneal cultures, septic complications[8] and development of postoperative abscesses[9].

Limiting surgical delay for PPU can be accomplished in a number of ways. After ruptured aortic aneurysm, PPU accounts for the highest mortality rate after emergency surgery overall[26]. Surgery for PPU should thus have a very high priority[24].

Respiratory and haemodynamic pre-emptive optimization (goal-directed resuscitation before surgery) reduces surgical mortality and morbidity in high-risk patients[27]. Implementation of a perioperative care protocol based on the Surviving Sepsis guidelines[11], including goal-directed resuscitation, improved 30-day survival in a PPU cohort[10]. However, the duration of optimization should be minimized to reduce surgical delay.

The results of the present study contrast with those of a randomized trial of surgery *versus* no surgery for PPU[28]. Morbidity and mortality rates in the two groups were similar in this small study of 83 patients, but the duration of hospital stay was increased significantly in the no-surgery group. The quality of evidence for non-surgical treatment is low[29] and the World Society of Emergency Surgery still recommends surgical treatment for PPU[30].

Disclosure

The authors declare no conflict of interest.

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Snapshots Quiz

Snapshot Quiz 13/32

Question: What is this condition and how should it be treated?

a **b** **c**

The answer to the above question is found on p. 1107 of this issue of *BJS*.

Huang K-C, Liang J-T: Division of Colorectal Surgery, Department of Surgery, National Taiwan University Hospital and College of Medicine, 7 Chung-Shan South Road, Taipei, Taiwan (e-mail: jintung@ntu.edu.tw)

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