

Delay in source control in perforated peptic ulcer leads to 6% increased risk of death per hour; a nationwide cohort study.

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Abstract

Aims

Delay to theatre for patients with intra-abdominal sepsis is cited as a particular risk factor for death. Our aim was to evaluate the potential relationship between hourly delay from admission to surgery and postoperative mortality in patients with perforated peptic ulcer (PPU).

Methods

All patients entered in the National Emergency Laparotomy Audit who had an emergency laparotomy (EmLap) for PPU within 24 hours of admission from December 2013 to November 2017 were included. Time to theatre from admission was modelled as a continuous variable in hours. Outcome was 90-day mortality. Logistic regression, adjusting for confounding factors was performed.

Results

3809 patients were included, 90 day mortality rate was 10.61%. Median time to theatre was 7.5 hours (IQR 5- 11.6 hours.) The odds of death increased with time to operation once adjustment for confounding variables was performed (per hour after admission adjusted OR 1.04 95% CI 1.02-1.07). In patients who were physiologically shocked (N=334), there was an increase of 6% in risk adjusted odds of mortality for every hour Em Lap was delayed after admission (OR 1.06 95% CI 1.01-1.11).

Conclusions

Hourly delay to theatre in patients with PPU is independently associated with risk of death by 90 days. Therefore we suggest that surgical source control should occur as soon as possible after admission regardless of time of day.

Introduction

Emergency Laparotomy (Em Lap) is performed to treat a range of intra-abdominal pathology [1–3] from intestinal obstruction to a perforated viscus. Thirty-day mortality for Em Lap in the England and Wales has decreased over the last four years from 11.7% in 2013 to 9.5% in 2017 [4]. However, higher mortality rates (17–34%) are seen following Em Lap performed for intra-abdominal sepsis compared to procedures without intra-abdominal contamination [4].

Sepsis is a leading cause of death in patients requiring Em Lap; 30–50% of patients have systemic inflammatory response syndrome, sepsis, or septic shock at first presentation to hospital [4, 5]. Treatment for patients with intra-abdominal sepsis includes timely administration of broad-spectrum antibiotics and timely source control. Timeliness of antibiotic therapy in sepsis has been investigated extensively [6–9], but less so the timing of source control. A small study of 154 patients from Japan suggested that, in those with gastrointestinal perforation associated with septic shock, time to operation was significantly associated with 60-day survival and quoted a survival rate of 0% if patients had their operation more than six hours after admission [10]. However, a larger population-based cohort study from Denmark examined a heterogeneous group of patients having emergency laparoscopy and laparotomy and concluded that there was no association between mortality and surgical delay when risk adjusted analysis was performed (odds ratio (95% CI) 1.003 (0.989–1.017) [11]. A paper using The Danish Clinical Register of Emergency Surgery, exclusively examined patients with perforated peptic ulcers who had emergency surgery. They concluded that every hour that elapsed between admission to hospital and operation was associated with a 2.4% increased chance of death at 30 days [12].

The conclusions of reports on delay to theatre are unclear. The aim of this study was to investigate the relationship between time to Em Lap for patients with perforated peptic ulcer disease and post-operative mortality using a large, prospective dataset of surgical cases collected in England and Wales.

Methods

Study Population

Adult patients who had an Em Lap for perforated peptic ulcer disease and were entered into the National Emergency Laparotomy Audit (NELA) database between December 2013 and November 2017 were included. Patients with perforated peptic ulcer were selected for investigation as this pathology is associated with peritoneal contamination leading to intra-abdominal sepsis [13]. Patients who had perforations from other sites in the gastrointestinal tract were not included as these could have resulted from pathologies where the accepted timing of surgery in relation to initial presentation is not always so clear cut. (For example, colonic perforations from progressing diverticular disease). Patients were excluded if they had their operation more than 24 hours after admission. This was to avoid bias caused by failure of an initially conservative management or a delay in intra hospital referral. Patients who had Em Lap for other complications of peptic ulceration were not included.

Study Variables

The main explanatory variable investigated in this study was time to theatre. Time to theatre was calculated in hours, using time of admission and time into theatre and was modelled as a continuous variable. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [14] were used to define tachycardia (HR>90 beats per minute), hypotension (SBP <100mmHg), physiological shock (HR >90 and SBP <100mmHg) and raised lactate (serum blood lactate >2.0 mmol/L). **All categories of shock (septic, hypovolaemic, cardiogenic etc) are included in the classification of “physiological shock”**. When selecting patients with each of the derangements (e.g “tachycardia” etc) no limit was placed on the other physiological parameters. **Physiological parameters were recorded in the pre-operative period.**

The following variables were extracted; age, sex, American Society of Anaesthesiologist (ASA) grade, urgency category at time of case booking, pre-operative Electrocardiogram (ECG) findings, pre-operative cardiac signs, respiratory history, pre-operative serum creatinine, pre-operative serum urea, pre-operative serum sodium, pre-operative serum potassium, pre-operative serum white blood cell count, pre-operative heart rate, pre-operative systolic blood pressure, pre-operative Glasgow Coma Score (GCS). We deemed it more clinically relevant to use post-operative values for intra operative blood loss, peritoneal soiling, operative severity and malignancy. The above data was used to calculate the NELA risk score for each individual [15]. We also extracted grade of operating surgeon and anaesthetist and whether the patient was directly admitted to a critical care unit post operatively.

Outcome measures

Outcome of the study was all cause 90-day mortality from the date of the index surgical procedure. Mortality within these timeframes was captured through established dataset linkage of NELA with the Office for National Statistics (ONS) death register.

Statistical analysis

Descriptive results are presented as mean (\pm standard deviation), median (IQR) or number (%) as appropriate. To test the association between time to theatre and postoperative mortality, we performed logistic regression. We present both unadjusted odds ratios (OR) and OR adjusted for the following selected covariates: NELA risk score, grade of operating surgeon and anaesthetist and admission to critical care unit post operatively. Structural factors were not included in the risk adjustment model because previous analysis of NELA data demonstrated no increase in mortality associated with case volume, hospital size or hospital configuration [16]. Results are presented with 95% confidence intervals (CI).

Subgroup analyses included patients with pre-operative tachycardia, pre-operative hypotension, pre-operative raised lactate, pre-operative physiological shock. We conducted all analyses using Stata Version 15 (StataCorp, College Station, Texas.)

This manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [17]. This analysis was performed as part of the National Emergency Laparotomy Audit (NELA) Collaboration's

remit to understand and improve the care of patients having emergency laparotomy and was approved by the Health Care Quality Improvement Partnership (HQIP.)

Results

Cohort description

The study cohort contained 4067 patients who had an Em Lap or Emergency Laparoscopy and repair of perforated peptic ulcer disease within 24 hours of admission. Patients with clinically recorded time to theatre of less than 30 minutes were not included as this was felt to be unrealistic (12 patients; 0.3%). Patients with missing mortality data (87; 2.1%) or variables required for risk adjustment (159; 3.9%) were excluded. This left a total study cohort of 3809 patients available for analysis.

The clinical characteristics are shown in Table 1.

Time of admission and time to theatre

The numbers of patients admitted with perforated peptic ulcer disease during the day was reasonably stable, with a slightly greater number occurring in the 12 hours between 12:00 and 23:59 (0800-1159; 631 (16.6%), 1200-1759; 1064 (27.9%), 1800-2359; 1070 (28.1%) and 0000-0759; 1044 patients (27.4%)).

Figure 1 demonstrates the time from admission to theatre for the cohort. The median time to theatre was the greatest (8.05 hours) in those admitted between 0000-0759 hours. In those admitted from 0800-1159, median time to theatre was 7.3 hours (Figure 2).

Outcomes

Crude 90-day mortality was 10.6%. Unadjusted odds of death by 90 days increased by 3% for every hour surgery was delayed after admission (unadjusted OR 1.03, 95% CI 1.01-1.05). This association remained with confounder adjustment (OR 1.04, 95%CI 1.02-1.07) with an increase odds of mortality of 4% per hour of increasing time from admission to theatre (Table 2). When dividing time to theatre into quartiles, in patients who arrived to theatre in the quickest quartile group (within 5 hours of admission) the mortality rate was 9.6%. This compares to 13% in the patients who had their operation within the slowest quartile (>11.5 hours) of study cohort.

We investigated the relationship between time to theatre and mortality in patients with each of the pre-operative physiological derangements defined previously. On adjusted analysis, death by 90 days increased by 4% for every hour after admission a patient arrived in theatre in those with pre-operative tachycardia (n=2298, adjusted OR 1.04 95% CI 1.02-1.07, Table 3). In those with hypotension before operative intervention (n=474), a 5% increase in the odds of death by 90 days per hour delay to theatre was seen (n=474, adjusted OR 1.05 95% CI 1.01-1.09, Table 3). A serum blood lactate of >2.0mmol/litre was recorded in 2372 patients before surgery and was associated with an increase odds of death by 90 days of 3% per hour post admission (Table 3).

Pre-operative physiological shock was present in 334 patients. In this group, unadjusted death at 90 days increased by 4% for every hour delay in reaching theatre. This increase remained at 6% odds of death per hour delay after adjustment for confounders (OR 1.06 (95% CI 1.01-1.11) (Table 3.)

Discussion

This is the largest study to date investigating the association between time to theatre and post-operative mortality in patients with perforated peptic ulcers. We report 90 day mortality of less than 11% in patients who have an Em Lap for perforated peptic ulcer disease in England and Wales. This compares favourably to studies from mainland Europe where death by 90-days are reported between 19.2% and 29.8% [18, 19].

When analysing the whole cohort, we found that adjusted odds of death increased as time to theatre rose, 3% per hour delay to theatre. These figures demonstrate that a patient (regardless of pre morbid state) who arrives in theatre within 6 hour is 18% more likely to die by 90 days compared to a patient who has their operation within 1 hour. Similarly patients who waited to 12 hours to arrive in theatre are 36% more likely to die than those who have expedited operative intervention.

Our findings reflect those of Buck et al who analysed a similar cohort of patients having Em Lap exclusively for perforated peptic ulcer disease from Danish registry data. They reported a decreased probability of survival by 2% for every hour delay in reaching theatre [12]. However, they did not describe how they calculated time from admission to surgery and included patients who had their operation more than 24 hours post admission which may be a reflection of the limits of registry data and bring confounding elements. Additionally in their risk adjustment, they reduced continuous variables such as age and shock to dichotomous outcomes, giving a less rigorous model.

Severity of physiological derangement varies among patients with PPU but its presence is important and urgent source control all the more important in those cases. We examined patients with pre-operative physiological derangement and suggest that there is an increased odds of death across all of the physiological derangement subgroups (Table 3.) The largest effect is seen in the group of patients who have pre-operative shock; 6% increased odds of 90 day mortality per hour delay on adjusted risk analysis. Our findings demonstrate that even in those patients that arrive in theatre within 3 hours of admission, their risk of death is 18% higher than those within one hour. This is in keeping with a report from Japan which found that survival rate fell for every 2 hours delay to theatre [10]. While not exclusively examining patients with perforated peptic ulcer disease, the Japanese study had a robust protocol with all patients having gastrointestinal perforation confirmed on Computerised Topography (CT) scan associated with septic shock. Additionally they report that none of their patients who had their operation greater than six hours post admissions survived to 60 days. **This may differ from our results due to the inclusion of patients with all forms of gastrointestinal perforation. Inclusion of those with faecal peritonitis may have contributed to the higher mortality rate by six hours.**

We have demonstrated that delay to theatre in patients with perforated peptic ulcer disease is independently associated with death by 90 days. Due to this, we suggest that patients with perforated peptic ulcer should have expedited access to theatre regardless of time of day. These patients should be treated with the same clinical urgency almost akin to

those with ruptured aneurysmal disease. It is well documented that those with ruptured aneurysms should take priority with regards to use of emergency staffing and operating space [20] and these cases are considered the most urgent within the surgical division. While hourly delay to theatre for ruptured aneurysmal disease has not been specifically described in the published literature, a crude mortality rate of 36% is reported [20], which is not dissimilar from our crude 90-day mortality rate of 31% in those with perforated PUD and pre-operative shock.

Additionally, our findings support the most recent clinical guidance from The Royal College of Surgeons (England) in the “High Risk General Surgical Patient: Raising the Standard” document. Recommendations from this include source control for patients with intra-abdominal sepsis complicated by septic shock should be within three hours and for those with sepsis without shock, arrival in theatre within in 6 hours [21].

We are not able to define the cause for delays to theatre as this is not collected by NELA, but patterns emerge. NELA demonstrates that delays incurred during the referral pathway from the Emergency Department to the point of senior surgical decision making also contribute significantly. Therefore, we advocate clear communication between Emergency department doctors and surgeons as well as sufficient prioritisation of surgical resources in the form of surgeon and theatre space to ensure timely care. A clear protocol can assist [22]. This is echoed by the key process measures recommended by the NELA reports; specifically that “prioritisation of access is given to emergency surgical patients ahead of elective patients whenever necessary as significant delays are common and affect outcomes.”

The strengths of this study are that it is a nationwide, multicentre centre, prospectively maintained database study linked with an externally validated mortality register. This is the largest study to date addressing this issue. The audit collects a wide range of variables and information allowing for confounder adjustment to be performed. We have performed risk adjustment for potential patient factors. This is in attempt to negate individual clinical patient factors (such as co-morbidity and age) that we know can impact on survival.

There are some limitations to this study. Case ascertainment was estimated at 65-70% in first two years of the audit [1, 2], which may have led to under or overestimation of adverse outcomes. Case ascertainment rates have increased subsequently. **NELA does not collect data on duration of symptoms prior to presentation to hospital. However, with the nature of perforated peptic ulcer disease, patients describe a sudden onset dramatic pain which in most cases would necessitate an expectant attendance at a healthcare setting. These clinical features should reduce variation in presentation time, perhaps in comparison to alternative conditions such as a small pulmonary embolism which may only led to subtle feeling of shortness of breath. Currently NELA, does not gather information on the methods and means of fluid resuscitation in the perioperative period. However, a large multicentre trial addressing this issue is currently taking place in England and Wales [23] which may led to the introduction of a nationwide resuscitation protocol for Em Lap patients.** Alternatively, if there was improvement after resuscitation there may be some over estimation of risk and this could dilute the effect of other factors in the risk adjustment

model. In the fourth year of NELA data collection, questions on timing of antibiotic administration were introduced. We were not able to include antibiotics in the risk adjustment model due to large amounts of missing data. It is hoped that with increasing awareness of the importance of antibiotics that data quality will improve in the next year of data collected to allow for further work in this area. This is an observational study and results can be suggestive of associations but not causality whilst the possibility of residual confounding cannot be excluded.

Conclusion

Mortality by 90 days is independently associated with time from admission to hospital to arrival in theatres for source control among patients with perforated peptic ulcer disease. The risk increases on an hourly basis and the greatest risk of death was seen in patients with shock. We suggest that clinical teams should strive to get all suitable patients with perforated ulcer to theatre as soon as possible regardless of time of day due to rising mortality per hour.

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