

Perioperative treatment of patients undergoing acute high-risk abdominal surgery

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THE 4 ORIGINAL PAPERS ARE

1. Tengberg LT, Cihoric M, Foss NB, Bay-Nielsen M, Gögenur I, Henriksen R, Jensen TK, Tolstrup MB, Nielsen LB. Complications after emergency laparotomy beyond the immediate postoperative period - a retrospective, observational cohort study of 1139 patients. *Anaesthesia*. 2017 Mar;72(3):309-316.
2. Tengberg LT, Bay-Nielsen M, Bisgaard T, Cihoric M, Lauritsen ML, Foss NB; AHA study group. Multidisciplinary perioperative protocol in patients undergoing acute high-risk abdominal surgery. *Br J Surg*. 2017 Mar;104(4):463-471.
3. Tengberg LT, Foss NB, Lauritsen ML, Orbæk J, Rod MH, Tjørnhøj-Thomsen T, Veyhe L, Bay-Nielsen M. The impact of acute high-risk abdominal surgery on quality of life in elderly patients. *Dan Med J*. 2017 Jun;64(6).
4. Jønsson LR, Ingelsrud LH, Tengberg LT, Bandholm T, Foss NB, Kristensen MT. Physical performance following acute high-risk abdominal surgery: a prospective cohort study. *Can J Surg*. 2017 Dec 1;60(6):12616.

Introduction

On Christmas morning, on a table in a private house in Kentucky in 1809, the 38-year-old pioneer surgeon Ephraim McDowell performed the very first successful laparotomy. All previous attempts had fatal results, where patients, initially surviving the procedure, died from sepsis or bleeding in the postoperative period. This time, the patient recovered successfully, despite the lack of anesthetic and antisepsis⁵.

Today, over 200 years and millions of procedures later, undergoing laparotomy is still associated with a great risk of postoperative complications and death, especially when performed as an emer-

gency. Emergency surgery procedures, account for a small fraction of all surgical procedures, but for a disproportionately large amount of the postoperative deaths⁶⁻¹⁰. In a population dominated by vulnerable, frail and comorbid elderly people with a high frequency of hypovolemia, hypoxia, sepsis, and most often severe pain, the perioperative treatment is complicated¹¹⁻¹³. These patients are further challenged by the risk of diagnostic delay, surgical delay, inadequate monitoring, and inadequate resuscitation. Even inadequate provision of critical care resources in these patients has been described⁸.

International reports suggest that the short-term mortality rate after emergency laparotomy is 15-25%, with great variation depending on selection criteria and facilities^{11,14-18}. In the United Kingdom alone, variation in short-term mortality rate extends between 4-42% in 35 National Health Service (NHS) hospitals¹¹. The outcomes in the ever growing population of elderly and frail undergoing emergency surgery are especially poor, with mortality rates exceeding 40%¹⁹⁻²¹ and a high risk of postoperative disability²². Patients undergoing major emergency surgery very seldom die in the operating room during surgery, but do so following a cascade of postoperative adverse events^{6,23-25}. While successful surgery is an obvious necessity for a good outcome, the technical skills in the operating room alone are not sufficient^{14,26}. The surgical treatment should be supplemented by high-quality perioperative care, ideally performed by multidisciplinary teams^{23,27-30}, motivated and trained to identify and handle complex medical challenges related to the surgical treatment³¹. While perioperative pathways in elective surgery has been optimised, introducing enhanced recovery regimens with multidisciplinary setups^{28,32,33}, the traditional perioperative treatment of patients undergoing emergency surgery is often a non-standardised practice. The common major emergency procedures and their consequences represent a massive healthcare burden^{34,35}, and there is tremendous potential for quality improvement.

Aim

This thesis aimed at describing the perioperative course and outcome of patients undergoing acute high-risk abdominal (AHA) surgery and to examine the effect of a standardised, multidisciplinary, perioperative protocol. Secondly we aimed to explore the mobility and long-term outcome, including self-reported health related quality of life, in subpopulations of patients treated according to the standardised protocol. Specifically, the objectives of the studies included in this thesis, was to investigate:

- The mortality-rate as well as the timing and frequency of postoperative complications following AHA surgery in 4 hospitals in the Capital Region of Denmark (Study I).

- The effect of a standardised multidisciplinary perioperative protocol with consultant-led care on outcome in patients undergoing AHA surgery (Study II).
- The physical performance and factors restricting physical performance postoperatively in patients undergoing AHA surgery (Study III)
- The quality of life, and residential status in elderly patients 6 months after undergoing AHA surgery (Study IV).

Background

Patients requiring immediate or urgent surgical intervention are a heterogeneous population with diverse underlying pathology. Absence of consensus on definition of the population of highest risk in emergency surgery compromises comparison of studies and outcomes. Traditionally, studies with focus on emergency surgery patients with poor outcome, included patients undergoing emergency laparotomy, defined as urgent, emergent, and immediately indicated open intra-abdominal surgery^{11,12,16,20,36–40}. In the United Kingdom the term emergency laparotomy has lately been accepted in several studies to include major emergency surgery performed both laparoscopically and open^{17,41,42}. In the retrospective Study I we adapted this terminology¹. Finally, a large group of emergency surgery studies have expanded inclusion criteria, including various combinations of major and minor emergency surgery procedures such as appendectomies, hernia without incarceration and cholecystectomies^{24,43–50}. Acute-onset of abdominal pain, in combination with clinical findings suggestive of major intra-abdominal pathology, traditionally resulted in an exploratory emergency laparotomy. Today, surgical management strategies have been developed and are no longer limited to a laparotomy. Laparoscopy has become widely accepted in major emergency surgery, both as a diagnostic tool and in management^{51,52}. Addressing management of major intra-abdominal pathology, without including both open and laparoscopic approaches, is no longer clinically meaningful.

We introduced the term AHA surgery, defined as major abdominal pathology requiring urgent emergency laparotomy or laparoscopy, including reoperations after elective gastrointestinal surgery and reoperations after previous non-AHA surgery, with the main categories being perforated viscus, intestinal obstruction, bowel ischemia, and haemorrhage¹⁷, excluding minor emergency surgery such as uncomplicated appendectomies, negative laparoscopies/laparotomies, cholecystectomies, sub-acute surgery (defined as planned to be performed within 48 hours), and also excluding pregnant women, traumas, urogenital, gynecological, and vascular pathology, except for acute mesenteric ischemia, treated by gastro-intestinal surgeons in Denmark.

Acute high-risk abdominal surgery in Denmark

The annual incidence of AHA surgery in Denmark is currently unknown. All emergency surgery patients are treated in public tax-financed hospitals. Admissions are registered with the International Classification of Diseases, version 10 (ICD-10). Surgical procedures are coded with the Nordic Classification of Surgical Procedures (NCSP), monitored in the Danish National Patient Register (NPR)⁵³. Nevertheless, the high number of different procedures and underlying diseases in combination with imprecise coding, challenges the overall view of the population. In Denmark, there is no organised national clinical register parallel to the National Emergency Laparotomy Audit (NELA) established in the United Kingdom in 2011, which includes major emergency

open-, laparoscopic- or laparoscopically-assisted procedures, with comparable inclusion criteria to the above mentioned for AHA surgery (www.nela.org.uk). We do, however, have a national register for peptic ulcer disease. Approximately 5-10% of the patients undergoing AHA surgery can be estimated to suffer from a perforated peptic ulcer^{16,54}. The Danish Public Health Authorities has founded the Danish Clinical Register of Emergency Surgery in order to monitor the treatment and outcome in patients presenting with bleeding or perforated peptic ulcer, as a part of the Danish National Indicator Project^{55,56}. Reporting is mandatory, with true reporting rates around 80-90%. In recent years, the national unadjusted 30-day mortality rate after operation for perforated ulcer has been more or less steady at 20%^{57–60}. There are several national reports concerning subpopulations of the patients undergoing AHA surgery^{37,48,61,62}, of which the majority concern surgically treated perforated ulcer disease and are based on data from the Danish Clinical Register of Emergency Surgery^{63–70}. All of the studies show high mortality rates, in most cases exceeding 20% (table 1, overview). As a consequence of the recognised challenges, a few intervention studies^{49,71,72} and a quality of care initiative⁵⁵ have commenced, none of them with a significant effect on long-term mortality^{73,74}.

Table 1. Overview of 30-day mortality, reported in patients undergoing subcategories of AHA surgery in Denmark

Papers	Inclusion criteria, year	n	30-day mortality, %
Sørensen et al ⁶¹ <i>Journal of Gastrointestinal Surgery, 2007</i>	Open abdominal surgery including appendectomies and cholecystectomies, 1995-1998	1867	13.8
Svenningsen et al ³⁷ <i>Danish Medical Journal, 2014</i>	Primary explorative laparotomy, 2010-2011	131	Overall: 23.7 <75 years: 10.6 ≥75 years: 47.8
Vester-Andersen et al ⁴⁸ <i>British Journal of Anaesthesia, 2014</i>	Patients undergoing AHA surgery + umbilical and ventral hernia without strangulation, 2009-2010	2904	Overall: 18.5 >80 years: 38.1
Danish Clinical Register of Emergency Surgery, period of registration:	Patients undergoing laparoscopic or open repair of perforated peptic ulcer		
2011/2012 ⁵⁷		333	22
2012/2013 ⁵⁸		384	21
2013/2014 ⁵⁹		272	14
2014/2015 ⁶⁰		276	22

Care-bundles

The Surviving Sepsis Campaign⁷⁵ is probably the most acknowledged care-bundle approach in emergency medicine. In patients with severe sepsis or septic shock it is estimated that up to 30% has an acute abdominal infection, many of them needing emergency surgery^{76,77}. Early administration of broad-spectrum antibiotics and source control is associated with a higher chance of survival^{78,79}. Very few emergency surgery studies have a focus on initial and standardised approach to patients undergoing AHA surgery^{71,80}. Evidence of optimal preoperative treatment and timing for surgery is lacking and a non-standardised practice is common. The challenges are being debated worldwide^{81–87}.

In trauma care, tradition and approach differs from the practice in emergency surgery, despite facing some comparable challenges. In trauma, specific diagnosis, procedure and pathology are not of highest priority initially. A systematic approach and training program in the management of trauma are adopted in more than 40 countries⁸⁸, well-known as the advanced trauma life support (ATLS) program⁸⁹. Widely accepted, but never tested in a con-

trolled clinical trial⁹⁰, the program systematically focuses on prompt systematic treatment of life-threatening injuries, initially ignoring lack of definite diagnosis, balancing stabilization and diagnostics. In the primary assessment (primary survey), the main purpose is to identify life-threatening injuries simultaneous with initiation of resuscitation. The physiological challenges in major emergency surgery are primarily sepsis, hypovolemia, pain and occasionally anemia due to bleeding or preexisting disease. The physiology underpinning these challenges is very disparate, but, inspired by the approach to trauma, the systematic standardised approach addressing monitoring, resuscitation and attention to the underlying problem should not necessarily be⁹¹.

Care-bundles introduced for patients undergoing acute high-risk abdominal surgery

In Denmark, the concept of care-bundles in emergency surgery was adapted in the multicentre PULP trial (2008-2009), where a perioperative protocol, based on the Surviving Sepsis Guidelines, was introduced to patients surgically treated for perforated peptic ulcer⁷¹. It showed promising results with a significant reduction of 30-day mortality compared to a historical control, but unfortunately there was no persistent effect on long-term mortality⁷³. In the United Kingdom the controlled multicentre ELPQuIC study (2012-2013) introduced a care-bundle, based on key recommendations with strong evidence from the Royal College of Surgeons of England and Department of Health, to patients undergoing emergency laparotomy⁸⁰, including admitting all patients to the ICU postoperatively. The care-bundle was associated with a significant reduction in the risk of death, defined as a lower number of deaths than expected, compared to a historical control. The reduction in crude mortality of 3.5% after implementation was insignificant. Also in the United Kingdom, the stepped wedge cluster randomised EPOCH trial is currently recruiting patients from at least 90 hospitals, to evaluate the effect of a perioperative care-bundle on 90-day survival following emergency laparotomy⁴².

Supplemental specific elements relevant to address in the perioperative care

Time to Surgery

In contrast to the surviving sepsis campaign, which recommends source control within 12 hours, the above mentioned trials recommended a time frame of a maximum of 6 hours from decision to operate to surgery. Setting proper time frames is a subject of debate^{62,68,92,93}. Some sense of urgency seems appropriate, despite lack of evidence of specific timing of surgery in most cases, except from mesenteric events and hemodynamic instability⁹³. Most hospitals are facing challenges in ensuring timely care of the emergency surgery patients, as a result of limited operating room capacity. Dedicated operating room capacity for emergency surgery patients has been shown to reduce cancellations and over-time^{94,95}, but there are no existing data on outcome.

Senior surgeon and anaesthesiologist

Urgent decision-making is central in treating patients undergoing AHA surgery, and competences of the responsible staff can be crucial for the outcome of these patients. Consultant-led care has indicated an improvement in outcomes in emergency surgery^{44,96} and in the light of the poor outcomes of the population, it seems reasonable to prioritise the presence of senior surgeons and anaesthesiologists. A recent study from the United Kingdom concluded that only 50% of all emergency laparotomies were carried out with both a consultant anaesthesiologist and a con-

sultant surgeon present. After 6 p.m. the proportion of emergency laparotomies receiving consultant-led care decreased. Defined best practice in the United Kingdom is presence of a consultant team in all cases with a predicted mortality higher than 10%¹¹.

Stroke-volume-guided hemodynamic resuscitation

Adoption of standardised stroke-volume guided resuscitation might be associated with reduced morbidity as it has been shown to be in elective high-risk surgery^{23,97-100}, and has been widely accepted as the standard of care in elective surgery¹⁰¹. The choice and amount of fluids is a subject of debate¹⁰²⁻¹⁰⁶. Studies from fluid resuscitation in ICU populations cannot and should not necessarily be applied to emergency surgery patients. Properly powered prospective trials comparing different fluid resuscitation strategies in surgical populations are needed.

Perioperative analgesia

Sufficient pain management and reduction of surgical stress can be successfully addressed with epidural analgesia and anesthesia when aiming for enhanced recovery after major surgery¹⁰⁷. The majority of AHA surgical procedures are laparotomies, causing considerable surgical injury, also increasing the risk of pulmonary complications¹⁰⁸. Epidural analgesia has also been shown to be protective against pneumonia following elective thoracic and abdominal surgery¹⁰⁹. Nevertheless, the use of epidural analgesia and anesthesia was not widespread for patients undergoing AHA surgery in 4 hospitals in Denmark (Study I). Epidural analgesia and anesthesia was introduced as the standard of care in the perioperative protocol in the AHA Study, in combination with early initiation of non-opioid analgesia (Study II).

Postoperative care pathways

Another subject of debate is the level of postoperative care. In general, there are 3 levels of care: standard ward care, intermediate care (organised as an independent unit or as a part of the intensive care unit (ICU) or post anaesthesia care unit (PACU)) and intensive care. The intensive care unit capacity and criteria vary enormously internationally^{110,111}. Several studies have shown an association between inadequate critical care resources and adverse outcomes^{8,9,14,48}, the most pronounced being the massive risk of death in high-risk surgical patients postoperatively initially admitted to the standard ward and then transferred to the ICU⁹. In Denmark and many other countries, there is no tradition of planned ICU care as a standard in emergency surgery, and admission is based solely on specific indication. Recently, a multicentre randomised controlled trial in Denmark (InCare Trial) aimed to evaluate the effect on 30-day mortality of intermediate care versus standard ward care following AHA surgery. Unfortunately the trial was stopped prematurely, showing no statistically significant effect on mortality in the enrolled patients⁴⁹.

Methodological considerations

General

There is a multitude of barriers in emergency surgery research. The unplanned nature and complexity in the consent process are some of the obvious ones. The need for well-conducted emergency surgery trials is undisputed. Randomised clinical trials (RCT) are widely accepted as the definitive method for clinical research¹¹². However, it is debatable if all emergency surgical research questions can be answered through RCTs. First, generalisability is dependent on how representative the study population is of the target population. Patient recruitment is often poor in emergency surgery studies as well as in trauma care research, due to both

surgeon and patient barriers¹¹³. Second, the complex challenges may not be covered by a simple hypothesis. The focus of traditional RCTs is evaluating simple therapies and to a lesser extent the delivery of care¹¹⁴. Despite the well-known risks of confounding and selection bias, well-conducted register-based cohort studies can reflect clinical practice and identify challenges in treatment and outcome¹¹⁵. Unfortunately, another problem is the poor tradition of emergency surgery registers. A pragmatic approach to clinical trials in emergency surgery is suggested to be relevant¹¹⁶, which was the procedure implemented in designing and conducting study II. A quality initiative aiming to improve the overall delivery of care requires multimodal interventions, parallel to the strategy in enhanced recovery regimens in elective surgery. The clinical impact is potentially high, but dependent on the availability of innovative research on the individual interventions and pathophysiology. It is well known from enhanced recovery protocols and other quality initiatives in elective surgery, that implementing multimodal perioperative standards into practice, is challenging. It involves motivation, buy-in and continuous guidance of involved team members including both surgeons, anesthesiologists, nurses, radiologists, physiotherapists, occupational therapists and secretaries and cannot be dictated by a simple written change in formal guidelines. In addition, when a massive focus is established in combination with a multimodal intervention, there is a risk of the attention alone being the primary cause of improvement in outcome (Hawthorne effect¹¹⁷).

Outcome measures

Mortality

The simplest possible outcome to measure and explain is patient mortality. In health care, reducing mortality is one of the most valuable goals, even though mortality is affected by other factors than quality of clinical care. Reporting of methods for analysis and potential biases are crucial for interpretation of results involving mortality as an outcome. We assessed the vital status of patients in all of our studies via the Danish Civil Registration System (CRS). Established in 1968 by the Danish government, the CRS is continuously updated with information on vital statistics¹¹⁸. A unique social security number is assigned to all individuals alive and living in Denmark, for administrative use. This unique system makes 100% follow-up on mortality possible.

Complications

There is no consensus on how to report adverse events in the postoperative course. The various definitions lead to confusion and challenges in comparison of studies. Many more or less validated systems exist. Our choice of reporting system was the Clavien-Dindo Classification system^{119–121}, describing 5 grades of severity for most known complications. The system has been validated in many studies across surgical specialties^{92,122–126}. Untraditionally, we chose to systematically register the timing of all postoperative complications 30 days postoperatively in our database, to be able to report the true overall morbidity and to be able to describe the time course of the postoperative deterioration.

Health related quality of life

There is an increasing and relevant focus on patient reported outcome measures (PROMs)¹²⁷. Surgeons' knowledge of the effect of emergency surgery procedures on patients' daily lives is very limited¹²⁸ and there are no known studies focusing solely on health related quality of life (HRQOL) in elderly undergoing AHA surgery. These outcomes are of special interest in this subpopula-

tion because there is an increased risk of poor outcomes and disability^{21,39}. In Study IV, we assessed patients' HRQOL using the validated SF-36 questionnaire¹²⁹ and compared them with an age-matched Danish background population. We also asked about residential status and formulated some additional, non-validated questions, regarding quality of life and buy-in for emergency surgery. We had no evidence of the relevance of the chosen supplemental questions.

Physical performance: uniaxial accelerometer ActivPAL™

In Study III, our aim was to describe the physical performance after AHA surgery to recognise the challenges we were facing. We specifically focused on examining early mobilisation, objectively. This was done by the use of the ActivPAL™ uniaxial accelerometer. The system is validated in older people with impaired function¹³⁰. We used the accelerometer as a single sensor placed on the thigh, limiting us in recognizing the change from lying to sitting in the bed. We combined the categories standing and walking, due to the known underestimation of actually walking at low walking speed, as expected when mobilised after undergoing AHA surgery¹³⁰.

Statistical considerations

In the studies in this thesis, we primarily used non-parametric statistics for continuous data and presented data as medians and interquartile ranges with nominal descriptive data as numbers (%). Comparison of paired data was made using Wilcoxon signed rank tests. An alpha level of 0.05 was used to indicate statistical significance, but the interpretation of the results should be seen in the light that the studies presented in this thesis are not based on randomization or random selection. The long-term survival of the cohorts in Study I and II was illustrated with Kaplan-Meier survival estimates and compared with the Log-rank test. In Study II, data were analysed with the intention to treat approach, meaning that all patients undergoing AHA surgery from the intervention cohort were included in the analysis, regardless of adherence to the study protocol. Logistic regression was used to adjust for differences in risk-factors in the cohorts with 30-day mortality as the dependent variable and a series of predefined characteristics as independent variables. We used 95% confidence intervals (CI) for proportions and odds ratios (OR). In Study IV SF-36 dimensions of the elderly survivors were compared with normative data from the age-matched Danish background population using a one-sample t-test. The p-values were Bonferroni corrected. Data were analysed using SAS® Enterprise Guide® 7.1, except from study III performed with SPSS version 19.

Presentation of the included papers

Study I

“High incidence of complications after emergency laparotomy beyond the immediate postoperative period”¹

Objective

We aimed to investigate mortality and morbidity after emergency laparotomy in the Capital Region of Denmark and to give a detailed description of timing, severity, and frequency of the complications in the postoperative course. In order to achieve this we manually systematically examined the electronic operation booking system and all electronic patient records from patients undergoing acute high-risk abdominal surgery and registered postoperative adverse events for 30 days. Long-term follow up on mortality was achieved from a national register of all citizens in Denmark.

Methods

The study was a population-based, retrospective, multicentre study, and involved all acute high-risk abdominal surgery patients aged 18 or above from 4 emergency surgical centres in the Capital Region of Denmark in 2012. The 1-year mortality data with 100% follow-up was retrieved from the Danish Civil Registration System¹¹⁸.

Results

A total of 1,139 patients were included. 47 % of all patients had a complication with a Clavien-Dindo Classification grade of 3 or higher within 30 days in a protracted pattern. The most common categories of complications were abdominal infection (19.7 %), pulmonary complications (19.3 %), and gastrointestinal complications (12.5 %). The median postoperative length of stay (LOS) was 11 days (IQR 6-24). The unadjusted 30 day mortality was 20.2%, and the 1-year mortality was 34 %: 60 % of the 30-day mortality happened later than 72 hours after surgery.

Conclusions

There is a prolonged period with a high frequency of complications and mortality after acute high-risk abdominal surgery. Reducing the risk of death and complications is a complex challenge. The perioperative treatment of patients undergoing acute high-risk abdominal surgery in the Capitol Region of Denmark was non-standardised. Perioperative standardised care bundles with risk stratification and strategies for prevention and treatment of complications are urgently needed.

Strengths and limitations

The overall limitation is that this study is merely descriptive and retrospective. The data are the first from Denmark, but the correlation between complications and poor outcome is well documented^{6,25,131}. Also, the Clavien Dindo Classification system has been used in other emergency surgery studies, but is not validated as such for emergency surgery patients. Our inclusion criteria for patients undergoing acute high-risk abdominal surgery arose from a clinically meaningful approach, including only patients with potentially life-threatening disease. The inclusion criteria are debatable and the lack of consensus on those internationally and nationally, challenges comparison of studies. We changed the terminology of the patient group in between Study I and Study II, but both studies have identical inclusion and exclusion criteria. The reason for the change was the need of a catchy phrase for the intervention study, where emergency laparotomy was outvoted due to the risk of misinterpretation of the inclusion criteria being limited to laparotomies.

The strengths of the study are the relatively large number of consecutive patients undergoing acute high-risk abdominal surgery in 2012, with a 100% long-term follow-up. To our knowledge, it is the first study describing the timing of postoperative complications, illustrating the protracted pattern in postoperative recovery after AHA surgery. This highlights the need for intensifying monitoring in the postoperative course, to facilitate early identification and treatment of postoperative complications. Additionally, it is a true population based multicentre study. The chosen method, using manual examination of the electronic patient records to identify documented adverse events and clinical consequences reduces the risk of underreporting complications¹³².

Study II "Reduced mortality after implementation of a multidisciplinary perioperative protocol in patients undergoing acute high-risk abdominal surgery. -The AHA study"²

Objective

Patients undergoing acute high-risk abdominal (AHA) surgery have a very high risk of poor outcome, with high rates of complications and death. There are numerous clinical, ethical and economic challenges related to the treatment of this group of patients and with an ageing population, the number of procedures is expected to increase. The aim of the present study was to evaluate the effect on mortality of a standardised perioperative protocol in patients undergoing AHA surgery, where implementation was achieved by focused multidisciplinary teamwork across all involved departments.

Methods

The study was a prospective single-centre intervention study in consecutive patients undergoing AHA surgery with a standardised, multidisciplinary, perioperative protocol implemented as standard treatment. AHA surgery was defined as major abdominal pathology requiring immediate emergency laparotomy or laparoscopy, including reoperations after elective gastrointestinal surgery. The intervention cohort was compared with a predefined, consecutive historical cohort from the same department. The data was analysed according to the intention-to-treat principles. The primary outcome was 30-day mortality.

Results

Baseline characteristics were comparable between the control and intervention cohorts. The most common indication for AHA surgery in both cohorts was perforated viscus (intervention 39%; control 39%) or intestinal obstruction (intervention 46%, control 47%). The unadjusted 30-day mortality was 15.5% in the intervention cohort compared with 21.8% in the control cohort (P=0.005). The 180-day mortality was 22.2% (intervention) compared with 29.5% (control, P=0.004). Median length of postoperative stay was 11 days (IQR 6-21; intervention) and 10 days (IQR 5-22; control, P=0.783). Median stay at the Intensive Care Unit was 3 days (IQR 1-9; intervention) and 5 days (IQR 2-17; control, P=0.018). In the intervention cohort, 38 % fulfilled the criteria for 24 hour postoperative intermediary care, which was performed in the post-anesthesia care unit.

Conclusions

The introduction of a standardised multidisciplinary perioperative protocol was associated with significant reduction in postoperative mortality and a changed pattern in the use of intensive care and intermediary care in AHA surgery patients.

Strengths and limitations

In the AHA study several methodological limitations need to be addressed. The main limitation is the study design. When choosing a non-randomised design, associations and trends can be shown, but it is impossible to test a cause- and effect hypothesis. On the other hand, it would have been unethical to use random allocation in a qualitative improvement study. If we, despite that, had chosen to randomize, there would have been a massive risk of a spillover effect. It is a single-centre study, and therefore, it is primarily a local evaluation of the protocol, and the external validity is limited. Also, in a non-randomised study, there is a risk of differences between patients in the 2 cohorts (selection bias). We had several initiatives to compensate for that challenge. First,

the cohorts were relatively large and included over limited time, reducing the risk of differences in demographics in between cohorts or changes in demographics in the area. Second, we had a predefined statistical analysis plan, analysing both unadjusted and adjusted mortality. We used a logistic regression model with the following variables, that are all known for potentially affecting outcome, as independent variables: primary pathology (perforation, obstruction or other), type of surgical technique (laparoscopic or open surgery), age, American Society of Anesthesiologists physical status classification grade, WHO/ECOG/Zubrod score, and presence of malignancy in the abdomen. We used 30-day mortality as the dependent variable. Finally, with a historical control, there is also a potential risk of time-based changes in treatment in the periods of inclusion (adoption bias). We tried to handle some of the expected changes. We hypothesized that we would increase the number of laparoscopic procedures in the intervention cohort, even though the protocol in itself did not interfere with surgical practice, and therefore this variable is included in the before mentioned logistic regression model. Also, a national screening for colonic cancer was initiated in 2014 for all citizens aged 50-74 years. Therefore we hypothesized that the acute debut of colonic cancer (obstruction or perforation) could be reduced and that was also incorporated in the adjusted mortality analysis (presence of malignancy in the abdomen). The strength of the study is the pragmatic and clinically highly relevant approach. It was a focused intervention addressing the perioperative standard practice. Also, the study population equals the target population and is analysed with an intention to treat approach, where all patients undergoing AHA surgery in the inclusion periods were analysed, not just the ones treated according to the protocol. Due to our functioning multidisciplinary cooperation and support from the heads of the departments, we had only very few cases, where we could not offer the protocol treatment, all due to lack of monitoring equipment in the first months of inclusion. The patients PACU stay was never rejected due to lack of capacity thanks to great flexibility, which is evidence of the general acceptance and motivation for the initiative. The design challenges are all known from enhanced recovery protocols in elective surgery, which despite these have gained wide acceptance during the last decades. In the implementation period of 9 months, there was great interest and motivation for changing and escalating care in accordance with the protocol.

Study III

“Functional performance following acute high-risk abdominal surgery – a prospective cohort study”³

Objective

There is limited knowledge regarding the postoperative physical performance of patients undergoing AHA surgery, and the factors restricting their performance. The degree of mobilisation is of interest, because physical activity is related to a reduction in the risk of especially pulmonary complications^{30,108,133}. Our aim in this study was to describe how much patients undergoing AHA surgery were mobilised the first postoperative week and to identify barriers to mobilisation.

Methods

This study was a single-centre prospective observational cohort study of consecutive patients undergoing AHA surgery from April 1st to May 31st 2014. The patients were treated according to a standardised, multidisciplinary, perioperative protocol, including a postoperative screening of all patients, to evaluate the need for physiotherapy and occupational therapy postoperatively. Func-

tional performance postoperatively was assessed on postoperative day 1 to 7, using the Cumulated Ambulation Score (CAS, 0-6) on a daily basis. The 24-hour activity level was measured using a thigh-worn accelerometer (ActivPAL™). Patients not independently mobilised, defined as CAS<6, were daily asked for a primary restricting factor.

Results

A total of 53 patients underwent AHA surgery in the study period, and 3 were excluded due to transfer to other departments or hospitals. Mean age was 61.4 years. Seven patients died within the first week postoperatively, and 33% of the patients were still not independently mobilised (CAS < 6) 7 days after surgery. The patients laid or sat more than a median of 23.4 hours daily within the first week after surgery and the main barriers to independent mobilisation were fatigue and pain. Even the patients who were independently mobilised, but still hospitalised, had a low median activity level of 1.5 hours per day on day 7 after undergoing AHA surgery in spite of attempts to enhance mobilisation.

Conclusion

Patients undergoing AHA surgery have limited functional performance in the first postoperative week, with a very low 24-hour activity level, despite daily visits from physio- and occupational therapists. These visits were prescribed in the standardised perioperative protocol along with standardised pain management with epidural analgesia 2 days postoperatively and an opioid-saving strategy with oral nonsteroidal anti-inflammatory drug (NSAID) starting the night before the epidural was removed. Important restricting factors for functional performance appeared to be exhaustion and pain. The effect of enhanced rehabilitation, including optimal pain and nutrition management, to increase the functional performance in these patients should be investigated. The effect of extending the amount of days with epidural analgesia and revising the oral pain management should also be investigated. Pain management, especially in the elderly patients, remains a challenge, mainly due to cognitive side-effects. Studies evaluating effect and tolerability of current and new drugs are still relevant.

Strength and limitations

The primary limitation of the study is the very small sample size and simple descriptive nature. It is a single-centre study, and we do not know if the results are generalisable or a measure of local conditions. The strength of this study is the first presentation of a surprisingly low level of mobilisation and activity in a large proportion of the patients, despite the initiatives in the standardised perioperative protocol. This lights the need for further postoperative intervention with an enhanced recovery program customised for these vulnerable patients. Further studies are needed to investigate the potential effects of further optimization of pain relief, nutrition, motivation, psycho-stimulating drugs, and physiotherapy on mobilisation.

Study IV

“The impact of acute high-risk emergency surgery on residential status and quality of life in elderly patients”⁴

Objective

Elderly people undergoing AHA surgery have an increased risk of experiencing death, complications and prolonged hospital stay. Yet, survival and complication rates are not necessarily adequate means for describing the life after major emergency surgery in the elderly. The aim of this study was to assess supplemental

patient centred outcome measures, by recording health-related quality of life (HRQOL) and residential status in patients ≥ 75 years, 6 months after major emergency surgery.

Methods

We performed a single center prospective study of elderly emergency surgery patients (≥ 75 years) undergoing AHA surgery between the 1st of November 2014 and the 30th of April 2015. Six months after surgery, patients completed a HRQOL questionnaire (SF-36) and an additional questionnaire regarding their physiological performance, residential status and motivation for undergoing emergency surgery in the future, if indicated. The patients HRQOL at follow-up were compared with 229 Danish age-matched controls.

Results

In the study period a total of 52 elderly patients underwent AHA surgery. Mortality rates were 33% 30 days postoperatively and 46% after 180 days. After 6 months 28 were alive and 22 (79%) participated in the follow-up. The majority of the survived elderly patients were willing to consent to surgery again, if necessary, but less willing than estimated by their closest relative. The overall quality of life was estimated as good in the majority. We found that all patients participating in the follow-up, were admitted from their own home and 21 out of 22 patients returned to living in their own home during the first 6 months after the operation.

Conclusions

Despite a high mortality, we, quite surprisingly, found a self-reported quality of life 6 months after AHA surgery, comparable with the background population, indicating a somewhat good recovery among survivors, and a high overall quality of life. The vast majority of the survivors had no loss of independence and they were willing to consent to undergo AHA surgery again.

Strengths and limitations

The main limitation is the relatively small sample size. Also, the use of a non-validated supplemental questionnaire developed by the authors specifically for this study, to investigate patient centred outcomes (PCO) in the elderly patients undergoing AHA surgery. There was a high degree of consistency between responses to the SF-36 and the non-validated questionnaire. Nevertheless, the conclusions based on the non-validated questions should be handled with precaution. It is not possible to test the HRQOL before emergency surgery due to unexpected nature of the disease, but it would have been desirable to do several reports in the postoperative course, to expand our knowledge of the self-reported rehabilitation process. Also, the combination with objective physical or cognitive measures is needed, and has been demonstrated to be informative of the rehabilitation process after major elective surgery by Lawrence et al¹³⁴. The strength of the study is the fact, that this is the first study on long-term patient-reported outcomes in a very vulnerable subpopulation of elderly patients undergoing AHA surgery. The ethical dilemmas, associated with the treatment of and communication with this patient subpopulation are numerous and any expansion of our knowledge concerning their outcomes and experiences associated with their care is useful. It is impossible to make conclusions from a study of this size, but it is helpful for further development in study design and hypotheses.

Discussion

Patients undergoing acute high-risk abdominal surgery have a ten-fold risk of death compared to patients undergoing elective high-risk procedures, such as colorectal surgery and coronary artery bypass surgery. Today, undertaking artery bypass surgery in the absence of a consultant surgeon and an available critical care bed would seem inconceivable. In contrast, Saunders et al showed that in the United Kingdom only 50% of all emergency laparotomies were carried out with both a consultant anaesthetist and a consultant surgeon present¹¹ and the use of intensive care postoperatively in Denmark is reported by Vester-Andersen et al to be as low as 16%⁴⁸, comparable with our findings of 24%¹. Through the four papers in this thesis we have investigated different aspects of treatment in acute high-risk abdominal surgery. The involved surgical procedures are common. By extrapolating data from Study I, the number of AHA procedures in Denmark can be estimated to be 3.000-4.000 per year. A number expected to increase with an ageing population. The benefits of initiatives to improve care are obvious both for society and the individual patient. There is a high risk of complications following acute high-risk abdominal surgery^{1,25,135} with a prolonged postoperative critical period of several days. The postoperative deterioration is often initiated by sepsis and/or cardio-pulmonary complications. The majority of postoperative deaths occurs following the immediate postoperative period¹. This indicates that there is potential for improvement in the perioperative, early and late postoperative course. In Study II we implemented a perioperative, standardised, multidisciplinary, multimodal protocol, to address the multiple challenges in treatment and outcome. Only two previous studies have investigated the effect of standardized, multimodal, multidisciplinary protocols^{41,71,73}. The results in Study II are more pronounced than in the existing studies from the United Kingdom and Denmark. This could be explained by the fact that the mortality before implementation of the protocol in Study II was higher in our centre, than in the four centres involved in the ELPQuIC study in the United Kingdom⁴¹ and the level of care possibly lower. The pronounced effect could also be due to the single-centre study design, where implementation and compliance to the protocol is easier to control. Interestingly, Study II is the first of its kind that has shown persistent long-term effects on mortality. All elements of the protocol were based on existing knowledge and recommendations, comparable to the intervention in the ELPQuIC study⁴¹ and the ongoing EPOCH trial⁴². Compared to the introduction of a single intervention, it requires behavioural change from the involved health care staff and continuous guidance. It is well known from enhanced recovery protocols and other quality initiatives in elective surgery, that implementing multimodal standards into practice is challenging and cannot be dictated by a simple written change in formal guidelines¹³⁶⁻¹³⁸. Implementation complexity and barriers are probably the main challenges that prevent optimal multimodal, multidisciplinary perioperative care from becoming widespread, but formal research into addressing and overcoming these barriers is sparse. Despite successful results in Study II, it is impossible to infer causality or to exclude attention bias¹¹⁷. In contrast to a randomized controlled study that investigates the efficacy of a single intervention in a controlled environment in a selected group of patients, Study II was a pragmatic trial aiming to improve clinical practice under day-to-day circumstances, showing the efficiency of the protocol. Both efficacy and effectiveness studies have strengths and limitations¹¹⁴. Further studies with different types of evidence is needed in order to raise the quality of patient care in emergency surgery. It is un-

known if the reduced mortality in the population in our department in simply represents a general national tendency. Approximately 5-10% of the patients undergoing AHA surgery have a perforated peptic ulcer requiring surgery. These patients are available for comparison in the Danish Clinical Register of Emergency Surgery. In Table 2 the 30-day mortality in patients following operation for perforated peptic ulcer in Copenhagen University Hospital Hvidovre is shown parallel to the 30-day mortality in all patients surgically treated for perforated ulcer in Denmark. Study II was initiated in June, 2013. The 30-day mortality rate in Copenhagen University Hospital Hvidovre, seems to have a decreasing tendency in this subpopulation of patients after implementation of the standardized multimodal protocol, compared to the general tendency nationally. The tendency should be interpreted with caution, since no formal statistical analysis has been made to compare the outcomes in Table 2. But in this register there are no signs of a general improvement of outcome nationally in patients undergoing surgery for perforated peptic ulcer.

Table 2. 30 day mortality in patients with surgically treated perforated peptic ulcer in Denmark and Hvidovre 2011-2015.

Danish Clinical Register of Emergency Surgery	30-day mortality in patients with perforated peptic ulcer (Denmark), % (95% CI)	30-day mortality in patients with perforated peptic ulcer (Hvidovre), % (95% CI)	Overall reporting rate = patients reported/ patients registered in NPR, %	Hvidovre reporting rate = patients reported/ patients registered in NPR, %
2011/2012 ⁵⁷	22 (18-27)	24 (13-40)	>90 (87-99%*)	96
2012/2013 ⁵⁸	21 (17-25)**	22 (10-39)***	<90 (83-94%*)	97
2013/2014 ⁵⁹	14 (11-19)	11 (2-29)	82	94
2014/2015 ⁶⁰	22 (17-27)	9 (1-29)	89	90

*Calculated on regional level

**In the original report from 2012/2013, the 30-day overall mortality was reported to be 19%. In the following reports this number is corrected to be 21%.

***In the original report from 2012/2013, the 30-day overall mortality was reported to be 21%. In the following reports this number is corrected to be 22%.

Following Study II, we described physical performance and barriers to mobilization following acute high-risk abdominal surgery. The patients were immobilized for a prolonged period following surgery. We had standardised the perioperative resuscitation, but we failed when it came to early mobilisation, despite increased attention and planned physiotherapy. The patient reported barriers were abdominal pain and fatigue. These challenges are well known and recognised in both elective and emergency surgery²⁷. Early mobilisation is essential for enhanced recovery and immobilisation is associated with pulmonary complications, loss of muscle mass and fatigue³³. Interventions facilitating mobilisation and rehabilitation in this population are needed. Obvious interventions that address barriers for mobilisation include management of pain, nutrition, postoperative delirium, and sleep disorders. Detailed studies investigating supplemental emotional barriers, such as fright in moving after major surgery could be relevant¹³⁹. The long-term physical effects of undergoing acute high-risk abdominal surgery were also measurable in Study IV, where elderly survivors reported a low score in the category "Role Physical", indicating challenges with daily physical activities. This is comparable to reports from the existing literature that state a physical recovery period in elderly following major abdominal surgery of more than 6 months^{22,134}. Surprisingly we recognised the elderly survivors to have an overall good quality of life, a positive finding in a subpopulation with prolonged hospitalisation and an increased risk of death and complications.

Conclusion and perspectives

Despite ten-fold higher mortality rates compared to elective high-risk patients, AHA surgery patients are being under prioritised in our health care system in many ways. There is a relatively low resource allocation involved in the care of these patients. The evidence for the optimal perioperative treatment of patients undergoing AHA surgery is still limited. Our studies support a strategy with a multidisciplinary standardised approach to the perioperative treatment of this vulnerable population with a high frequency of pain, hypovolemia, hypoxia and sepsis is beneficial. The limited knowledge of many elements in the extended rehabilitation period following acute high-risk abdominal surgery remains obvious. The primary focus of future studies should be prevention and treatment of postoperative complications. Specialised care in highly dedicated centres and wards with a multidisciplinary setup would provide the basis for implementing enhanced recovery beyond the immediate postoperative period and facilitate further valuable research in this population. Further research is needed in triage and risk stratification, investigation of plasma biomarkers for perioperative risk prediction, delirium and sleep disorders, but most importantly in further optimization of perioperative medicine and the processes of decision making in emergency surgery. We also tend to forget the palliative treatment of the inevitable dying patient. Last, but not least, an important step for Denmark in this area is the development of a national registry covering all emergency surgery. A national registry covering patients undergoing AHA surgery could provide the framework for a national strategy to improve care in these patients.

English summary

Critically ill acute high-risk abdominal surgery patients represent a major challenge to health care providers, with the typical patient being elderly and frail, and with severe and multiple comorbidities. The mortality rate in this population is high, and the postoperative course is characterized by complications, prolonged hospitalisation and considerable risk of permanent disability. With an ageing population, the number of elderly patients, as well as challenges concerning treatment will arise, calling for a coordinated effort both nationally and internationally to enhance treatment in this vulnerable patient group. By the time of admission, the acute high-risk abdominal surgery patients are often physiologically deranged. The burden of multiple organ system dysfunction caused by an acute abdominal catastrophe, is associated with great risk. Timely stabilisation, diagnosis, pain management and surgical treatment are essential for a good outcome. Except from a few initiatives in subpopulations, there has, up until now, been an absence of organised multidisciplinary collaboration in approaching the critically ill emergency surgery patient. We have not been able, neither nationally or internationally, to introduce a standardised approach to the perioperative treatment based on the existing evidence. By analysing data from 4 hospitals in Denmark, we were able to illustrate a protracted critical period following acute high-risk abdominal surgery, where the frequency of postoperative complications is high, and associated with an increased risk of dying. The mortality in the cohort was 34% one year after surgery. A standardised, multimodal and multidisciplinary perioperative treatment protocol was implemented at Copenhagen University Hospital, Hvidovre. This resulted in a significant and persistent reduction in mortality during a follow-up period of 6 months. Despite the standardised course, we recognised the difficulty in mobilising patients during the first postoperative week due to fatigue and pain. Traditionally, the

success in treatment is measured by death- and complication rates, and length of hospital stay, but the literature is sparse when reporting patient outcome measures. We found a surprisingly good quality of life in a small group of elderly patients who had survived acute high risk abdominal surgery. In the future, it is essential to use patients' knowledge and experience to develop quality improvement initiatives in treatment, as well as to improve the dialogue between the patient, doctor, and closest relatives, helping them in forming realistic expectations of the postoperative outcomes. Unfortunately, as of now, we have no systematic collection of patient reported outcome measures in this critically ill and rather vulnerable population. This is a challenging group of patients with a need for extensive treatment, and specialized care, and rehabilitation. Future research should be conducted in dedicated specialized wards, where the staff is educated and motivated to see the complicated task through. The initiative from the research group behind this thesis should be considered as a clinically relevant, pragmatic introduction to a hopefully larger and necessary effort to improve the quality of care and the outcome following acute high-risk abdominal surgery.

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