Inflammation in ischemia and reperfusion: From mice to men

Diepenhorst, G.M.P.

Citation for published version (APA):
Diepenhorst, G. M. P. (2014). Inflammation in ischemia and reperfusion: From mice to men

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
ACUTE OCCLUSIVE MESENTERIC ISCHEMIA: PREDICTORS OF MORTALITY AFTER SURGICAL TREATMENT OF BOWEL NECROSIS
ABSTRACT

BACKGROUND: Acute arterial occlusive mesenteric ischemia (AOMI) consists of acute arterial thrombosis or embolism of the superior mesenteric artery and continues to pose a diagnostic and surgical challenge. Despite medical advances, mortality rates remain high, emphasizing the need for further insight into the disease and risk factors of mortality. This review examines our center’s experience in diagnosis and treatment of patients with AOMI who underwent surgery due to bowel necrosis and identifies diagnostic predictors of mortality in this patient category. We hence aimed to identify patients with AOMI requiring direct operative exploration. Furthermore, insight is given into changes in mortality rates throughout the study period in our institution.

METHODS: A retrospective review of patients between 1991 and 2010 identified patients with intra-operative and/or pathological confirmation of intestinal ischemia. Etiologic and clinical features, imaging studies, laboratory findings, pathological finding and surgical procedures were recorded and assessed as possible risk factors of postoperative mortality.

RESULTS: A total of 56 AOMI patients who underwent surgical treatment (20 males, 36 females) were included. Extensive bowel necrosis was found during laparotomy in 15 patients (27%), precluding further treatment options. Thirty patients underwent bowel resection only (54%) whereas 11 patients (20%) underwent a combined procedure of revascularisation and bowel resection. Diagnostic risk factors of mortality were age >70 years, anticoagulant use, diabetes mellitus, prior vascular surgery, peripheral vascular surgery, chronic obstructive pulmonary disease and prior myocardial infarction, elevated levels of amylase (>161 U/L) and AST (>47 U/L), shock and an ASA V classification (P<0.05).

CONCLUSIONS: Patients presenting with acute abdominal pain in combination with advanced age >70 years and/or multiple comorbidities including cardiovascular risk factors and diabetes mellitus should be considered highly suspicious of AOMI.
only. Hence, 56 patients were identified and classified as having AOMI based on imaging, the operation notes, pathological reports, or autopsy findings. Where descriptions were not clear or unavailable parameters were described as unknown. In this patient population of 56 cases of AOMI, diagnostic and treatment factors are summarized and diagnostic predictors of mortality are identified.

Statistical analysis
Postoperative survival was defined as survival in days after surgery until the last day of contact was used as a primary outcome parameter. Categorical variables are presented as frequencies and percentages of valid recordings. Continuous data are represented as mean +/- SD or median +/- IQR. Univariate analysis was performed using a Cox regression model using total days of survival to determine relevant risk factors as predictors of mortality. Variables were excluded when less than 50% of data was present and unknown data are excluded from the analysis. A value p<0.05 was considered significant. A Kaplan-Meier curve with Logrank test was used to determine differences in survival between time periods. According to the distribution of data, data were treated as parametric or non-parametric. Statistical analyses were performed using SPSS version 21.0 (SPSS Inc, Chicago, IL) with advice of a statistician.

RESULTS

Patient demographics
Between 1991 and 2010 56 patients with AOMI were identified meeting the inclusion criteria as defined in the methods section. The study population included 36 females (64%) and 20 males (36%) with a median age of 68 years (range 23-93). Based on radiological and pathological findings, the etiology was thrombotic occlusion in 61% (34/56) of patients and embolic occlusion in 27% of patients (15/56). Of 7 patients, the etiology was unknown. Relevant co-morbid medical conditions and risk factors are shown in Table I. The most common co-morbid medical condition was hypertension (45%), followed by anticoagulant use (34%), prior vascular procedures (21%) and history of arrhythmia (21%). Median hospital stay was 35 days (range 0-148 days). Patients with ASA classifications II and III demonstrated longer survival times (median 3409 and 238 days resp.) whereas none of the patients classified as ASA V survived 24 postoperative hours.

Clinical presentation
Most patients presented with symptoms lasting less than 24 hours (38%). Median duration of symptoms at presentation was 48 hours (range 4-408 hours). Abdominal pain was the most common presenting symptom (94%) followed by nausea (81%), vomiting (76%) and diarrhoea (50%). On physical examination, abdominal tenderness was observed most (94%) followed by peritonitis (65%), shock (21%) and abdominal guarding (21%). In patients in which details of the physical examination were described, 50% of patients presented with tachycardia (heart rate>100), whereas 36% demonstrated abnormal blood pressures and 10% presented with fever (>38.5°C).

Laboratory evaluation
All patients demonstrated elevated pre-operative CRP levels (>10 mg/L) (mean 168 mg/L). Elevated mean leucocyte counts were noted 94% of patients (mean 21 x 10^9/ml). Neutrophil counts were abnormal in 95% of patients (mean 83%). An elevated lactate level (>2mmol/L) was noted in 89% of patients (mean 6.4 mmol/l). Patients showed abnormal amylase levels (>161 U/L, mean 236 U/L) in 46% of the patients. Elevated levels of aspartate transaminase (AST) (> 47 U/L, mean 336 U/L) were measured in 28% of the patients.

Radiologic imaging
All patients underwent one or more diagnostic imaging tests, without use of a standard diagnostic algorithm. Diagnostic patterns changed measurably throughout time, with increasing use of CT scanning (29% of cases between 1991 and 1998 versus 89% of cases between 2005 and 2010) and decreasing use of abdominal radiography (86% 1991-1998; 44% 2005-2010) and ultrasonography (57% 1991-1998; 33% 2005-2010). Abnormalities such as bowel dilatation, free intraperitoneal air or intra-abdominal fluid were detected in
28% of abdominal ultrasonography cases and in 52% of plain abdominal radiographic images. However, the findings in these modalities mostly did not specify further. CT Angiography (CTA) scans were performed in 22 patients (39%) and 6 patients underwent conventional CT scanning (11%). In 58% of patients in whom CT scanning was performed, results were indicative of intestinal ischemia with visualization of suggestive signs of intestinal necrosis such as pneumatosis intestinalis, mesenteric infiltration, organ infarction, a thickened bowel wall, abnormal contrast enhancement of the bowel wall, intra-abdominal fluid or air (14/24 patients, 4 unknown). The number of vessels participating in the disease was reported in several radiological reports. However, reported numbers were too low to draw conclusions with respect to outcome.

Surgical interventions
Treatment factors related to surgical interventions are listed in Table II. When multiple surgical interventions were performed all were included in the analysis. Fifteen patients (15/56; 27%) underwent exploration only due to extensive bowel necrosis, which excluded any further treatment options during surgery. Most patients (n=30, 54%) underwent bowel resection only whereas in 11 patients (20%) a combined procedure of revascularisation and bowel resection was performed. Revascularisation procedures included bypass grafting (aorto-iliac-mesenteric) (5/56; 4%), or embolectomy, thrombectomy or endarterectomy with or without patch angioplasty (2/56; 4%) or a combined procedure of thrombectomy and a bypass procedure (2/56; 4%). As expected, the shortest median survival time was shown by patients not undergoing resection due to extensive bowel necrosis (24 hours), whilst the longest median survival time was demonstrated by patients undergoing a combined bowel resection and revascularisation procedure (371 days). When specifying which section of bowel was removed, a combination of a small bowel and colon resection was performed most often (20/56; 36%) followed by a small bowel resection (19/56; 34%) and colon resection only (1/56; 2%). At initial operation, a primary intestinal anastomosis was created in 27 patients (48%) while 9 patients (16%) received an ileostomy or colostomy. As may be expected, the longest median survival time was found in the group of patients undergoing a small bowel resection only (238 days) and in the group of patients in which the decision was made to create an intestinal anastomosis (788 days). After initial surgery, in 16 out of 30 patients undergoing a second operation, the operation was considered to be a "second look" operation (16/30; 53%). In 9 of these patients no intra-operative abnormalities were noted (9/30; 30%). Unfortunately, the relatively small patient category did not allow distillation on whether there was a difference in outcome depending on etiology (i.e. thrombosis or embolism).
Treatment outcome

The overall 30-day, 1- and 10-year mortality rates were 52%, 71% and 89%, respectively. Post-operative complications occurred in 48 out of 56 AOMI patients (87%, 1 unknown). Multi-organ failure was described in 11/56 (20%) of patients, postoperative bleeding in 8/56 (14%), sepsis occurred in 7/56 (13%) of patients, anastomotic leaks in 3/56 (5%) of patients, and short bowel syndrome in 4/56 of patients (7%). In the study, 1-year mortality rates remained high throughout past decades with 74% (23/31) in 1991-2000 and 68% (17/25) in 2001-2010. The Kaplan-Meier curve depicts mortality over the two decades (Figure 1), in which a better long-term survival is suggested in patients operated between 2001 and 2010 than in patients operated between 1991 and 2000 (non-significant).

Risk factor analysis

A univariate analysis was performed to determine relevant diagnostic risk factors as predictors of mortality, as depicted in Table III. Age >70 years increased the risk of postoperative mortality with a relative risk of 6.0 (P<0.00001, CI 2.7-12.1). The co-morbid factors identified as significant predictors of mortality were anticoagulant use (P=0.004; RR 3.7), prior vascular surgery (P=0.026; RR 2.6), diabetes mellitus (P=0.009; RR 3.3), ASA V classification (P=0.004; RR 5.6), prior myocardial infarction (P=0.005; RR 3.9), peripheral vascular disease (P=0.034; RR 2.5) and chronic obstructive pulmonary disease (P=0.038; RR 3.7). A clinical presentation with shock symptoms was identified to predict postoperative mortality (P=0.005; RR 3.5; CI 1.4-8.2). Duration of symptoms did not significantly influence postoperative mortality. Abnormal serum amylase (P=0.001; RR 5.1) and AST levels (P=0.048; RR 2.3) also predicted postoperative mortality. A correct diagnosis on radiological imaging did not successfully predict outcome in this study. As may be expected in a retrospective study, treatment factors were strongly associated with the type of patient category. Patients in which exploration only was performed demonstrated a significantly worse survival (P<0.000001; RR 10.7; CI 4.4-25.9). Patients in which bowel resection only was performed (P=0.021; RR 0.5; CI 0.2-0.8), a primary anastomosis was created (P=0.02; RR 0.2; CI 0.2-0.9), or only small bowel was resected (P<0.000001; RR 10.7; CI 4.4-25.9), represented a patient group with significantly better survival.

Figure 1. Survival using Kaplan-Meier analysis
DISCUSSION

Acute occlusive mesenteric ischemia (AOMI) remains a potentially life-threatening disease. In an effort to further expedite diagnostic work-up and treatment planning, we reviewed the surgical experience of the past two decades. Our study demonstrates several clinical factors predicting poor outcome, which are comparable with the international literature on this subject. Our mortality rates (30 day, 1- and 10-year mortality rates of 52%, 71% and 89%, respectively) are similar to cohorts described previously\(^{16}\). Our study demonstrates that, despite medical advances in diagnostic modalities and therapeutic strategies, including improved imaging, increased experience in surgical revascularization techniques and more advanced supportive intensive care, medical advances have not been translated into a decrease in mortality rates throughout this time period. Few studies have analysed patients with AOMI over a comparably long period of time whereas patients with mesenteric ischemia are known to often die from long-term complications\(^{10}\).

This study analyses a selected group of patients in an advanced stage of disease with intra-operative bowel necrosis due to AOMI in whom treatment with vasodilatation, anticoagulation or revascularisation only was not an option, representing a patient group with an advanced stage of the disease. Hence we attempted to create a relatively uniform group in a disease entity characterised by a widely variable patient category. By analyzing a patient group with an advanced stage of the disease we hoped risk factors to demonstrate a more pronounced effect. Patients with mesenteric venous thrombosis and non-occlusive mesenteric ischemia as underlying etiologies were excluded. Furthermore, non-surgical patients deemed difficult to capture in a retrospective approach using operative and pathological codes.

The risk factor profile of AOMI in this study includes the typical features of advanced age, cardiovascular disease and multiple comorbidities. Age was an independent risk factor of mortality in this study, in which patients older than 70 years demonstrated a 6-fold increased risk of mortality. Diabetes mellitus, anticoagulant use, prior vascular surgery, COPD, peripheral vascular disease, prior myocardial infarction and as ASA V classification at first operation were all identified predictors of mortality in this study. In concordance, guidelines for acute intestinal ischemia have identified patients with a history of cardiovascular disease to be at risk of acute intestinal ischemia, alongside patients developing acute abdominal pain after arterial interventions\(^{17}\). However, patients aged >70 years or patients with high ASA classifications may have received less aggressive treatment in this study group.

The aspecific nature of the clinical presentation in AOMI is emphasized by our study. Patients presented mostly with abdominal pain, often accompanied by nausea and vomiting. Physical examination mostly yielded abdominal tenderness, often accompanied by peritonitis. Shock, indicative of an advanced disease stage, was identified as a predictor of mortality. It is noteworthy that, in our population of patients with gangrenous bowel during operative exploration, only 65% of patients presented with peritonitis, 21% with shock symptoms and 21% with abdominal guarding, hence emphasizing the challenge of a diagnosis based purely on clinical presentation.

Numerous serum markers including D-dimer\(^{12-14}\), amylase\(^{15,16}\), alkaline phosphatase\(^{17}\) and lactate dehydrogenase (LDH)\(^{17,18}\) have been described to be potential diagnostic tests of mesenteric ischemia\(^{19,21}\). Lactate has traditionally been put forward as the best diagnostic markers for intestinal ischemia, as supported by a recent systematic review\(^{24}\). However, most markers including lactate have been found to be insensitive and nonspecific and none have proven reliable enough to diagnose acute mesenteric ischemia\(^{25}\). As predictors of mortality, lactate levels and marked leucocytosis at the time of diagnosis are prognostically unfavorable, although nonspecific, factors\(^{26-28}\). In our series, elevated mean leucocyte counts and elevated lactate levels were noted in 94% and 89% of patients respectively. However, only amylase and AST were demonstrated to be significant predictors of mortality, emphasizing the potential overlap in protein expression between liver and intestine, making it difficult to distinguish the specific organ of origin\(^{29}\). In general, markers for mesenteric ischemia appear only after transmural infarction has occurred, whereas the ideal laboratory test should detect ischemia before gangrene has developed. Enhanced understanding of the pathophysiology of intestinal damage has shifted the attention of researchers towards mucosal damage markers. Assays of novel markers such as intestinal fatty acid binding protein\(^{30,31}\) have shown some promise but were not routinely measured in our series and were therefore not analyzed.

Diagnostic imaging in AOMI has drastically changed in the last decade. Abdominal radiography and ultrasonography were both nonspecific and non-diagnostic in this study and are not considered appropriate diagnostic tools today. The high diagnostic accuracy of multidetector CT (MDCT) with intravenous contrast enhancement supports the switch from catheter-based angiography to multidetector CT as the first-line imaging method of choice in patients suspected of having primary AMI, due to better image quality, expansion of availability, and ease of noninvasive image acquisition\(^{32,33}\). Accordingly, an increasing use of CT is noted in our study, in which a CT scan is performed in 29% of patients between 1991 and 1998 versus 89% of patients between 2005 and 2010. Pneumatosis intestinalis, mesenteric infiltration, organ infarction, thickened bowel walls, abnormal contrast enhancement of the bowel wall or intra-abdominal fluid or air are noted as signs of intestinal necrosis in 58% of cases, confirming the ominous, although often non-specific nature of these findings in the diagnosis of AOMI as described in literature\(^{32,34}\).

Surgical treatment in this advanced patient category consisted of bowel resection only in most cases. As expected, patients undergoing bowel resection combined with revascularisation procedures demonstrated the highest postoperative survival, as these must have been patients with more favourable prognostic factors. In general, newer endovascular treatment options including catheter-directed thrombolysis and visceral vessel stenting are best used when the diagnosis is made early and bowel integrity has not yet been compromised and were therefore not included. Of further note is the finding that a “second look” operation yielded no intra-operative abnormalities in 30% of cases,
supporting the notion of the laparotomy-on-demand strategy\textsuperscript{35}. Survival analysis in our study suggests better long-term survival in patients treated in the recent decade when compared to those between 1991 and 2000 (non-significant). Of note is that mortality in this more recent group appears to occur at a later postoperative phase, which may in large part be related to improved supportive care. Hence the question arises whether better supportive care merely delays mortality in this patient category.

Admittedly, the retrospective nature of this study encompasses several limitations. First, the retrospective selection of patients using diagnostic codes, operative codes and pathology records may not have identified all cases of acute intestinal ischaemia, as the relatively low number of patients suggests. This may have magnified the effect of selection bias. Second, treatment was not randomized and followed the surgeon’s preference. Furthermore, only patients with a confirmed diagnosis of AOMI who underwent surgical intervention and required bowel resection were included; those who were deemed unfit for surgery or those who improved after treatment with vasodilatation, anticoagulation or revascularisation were excluded. Undoubtedly, exclusion of patients with early ischemia in whom revascularisation only was a treatment option has lead to a relatively high mortality rate in this patient group. Analysis of a cohort over an extensive period of time may raise questions on the application of the findings in the contemporary setting. However, the validity of the main findings of the study is supported by the largely unchanged basic pathological mechanism of the disease. A further study would undoubtedly require a larger patient group, acquired through a multicenter setup, to allow more specific analysis of risk factors using current diagnostic modalities and treatment and including patients undergoing thrombolytic therapy and revascularisation procedures.

Despite improved diagnostic modalities, increased awareness, improved critical care and more minimally invasive options AOMI remains a disease entity associated with potentially detrimental outcome. The initial clinical presentation is often nonspecific and misleading. To improve early recognition and potentially improve survival, patients presenting with acute abdominal pain in combination with advanced age >70 years and/or multiple comorbidities including cardiovascular risk factors and diabetes mellitus should be considered highly suspicious of AMI. Diagnostic studies should include MDCT scanning with appropriate intravenous contrast. Subsequent prompt intervention consisting of revascularization of ischemic tissue and resection of necrotic intestine remains essential to improve outcome.
REFERENCES


