ORIGINAL ARTICLE

The Value of Serial Serum Lactate Measurements in Predicting the Extent of Ischemic Bowel and Outcome of Patients Suffering Acute Mesenteric Ischemia

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Abstract

Background Acute mesenteric ischemia (AMI) is an emergency with a mortality rate up to 50 %. Detecting AMI continues to be a major challenge. This study assed the correlation of repeated preoperative serum lactate with bowel necrosis and to identify risk factors for a lethal outcome in patients with AMI.

Methods A retrospective study of 91 patients with clinically and pathologically confirmed AMI from January 2006 to December 2012 was performed.

Results In-hospital mortality rate was 42.9 %. Two hundred nine preoperative lactate measurements were analyzed (2.3 ± 1.1 values per patient). Less than or equal to six hours prior to surgery, the mean serum lactate level was significantly higher (4.97 ± 4.21 vs. 3.24 ± 3.05 mmol/L, $p=0.006$) and the mean pH significantly lower (7.28 ± 0.12 vs. 7.37 ± 0.08, $p=0.001$) compared to >6 h before surgery. Thirty-four patients had at least two lactate measurements within 24 h prior to surgery. In this subgroup, 17 patients (50 %) exhibited an increase, 17 patients (50 %) a decrease in lactate levels. Forward logistic regression analysis showed that length of necrotic bowel and the highest lactate value 24 h prior to surgery were independent risk factors for mortality ($r^2=0.329$).

Conclusion The value of serial lactate and pH measurements to predict the length of necrotic bowel is very limited. Length of necrotic bowel and lactate values are independent risk factors for mortality.

Introduction

Acute mesenteric ischemia (AMI) is a life-threatening condition, requiring immediate intervention to prevent severe abdominal complications and death. The reported mortality remains high, exceeding 50 %.[1] AMI accounts for approximately 0.1 % of all hospital admissions, with an increasing incidence in elderly patients.[2] Increasing the delay in the diagnostic process leads to a parallel increase in the mortality rate.[3] Complete disruption of the intestinal blood supply leads to irreversible mucosal ischemic damage within 6 h.[4]

Transmural bowel infarction presents with severe abdominal pain (94 % of patients) and is often accompanied by nausea, vomiting, bloody diarrhea, or grossly melanotic stool.[5] A pain-free interval of 4–6 h after the onset of the symptoms may be encountered and is partly responsible for delays in the patient's presentation and for diagnostic delays.[3] Detecting AMI remains a challenge and requires a high degree of suspicion, as the findings are nonspecific and there are no specific laboratory parameters.

Today, multidetector computed tomography (CT) scan is the standard diagnostic tool to detect AMI. The sensitivity (93.3 %) and specificity (95.9 %) of the CT for the diagnosis of AMI has matched the sensitivity of angiography (88 %).[6,7] Besides the patient's history of symptoms, clinical findings, and radiology, patients with AMI usually present with laboratory signs of marked inflammation, such as leukocytosis. In

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addition, metabolic acidosis may be present. All laboratory parameters tested so far have a poor sensitivity and specificity; however, no serial measurements have been analyzed so far.[8]

The aim of this study was to evaluate preoperative *serial* serum lactate and pH in patients suffering AMI. In addition, pre, intra, and postoperative patient characteristics were analyzed in order to identify risk factors for a lethal outcome. To the best of our knowledge, the assessment of serial serum lactate measurements and risk factors for lethal outcome in patients with AMI has never been done before.

Materials and Methods

A retrospective study was performed of patients with AMI confirmed by laparotomy and histology at Bern University Hospital, Switzerland, between March 2006 and December 2012. Patient characteristics were collected using a computerized spreadsheet (Microsoft Access 2003, Microsoft Corporation, Redmond, WA). The collected demographic and preoperative variables were as follows: age, gender, main diagnosis, body mass index (BMI), prior surgical procedures, smoking history, alcohol abuse, drug history (anticoagulants, platelet aggregation inhibitors, statins, diuretics, antihypertensive drugs), blood gas analysis (lactate, pH), serum markers (white cell count, C-reactive protein (CRP), history of arteriosclerosis, chronic cardiovascular disease, chronic pulmonary disease, pre-existing hepatological disease, diabetes mellitus, bowel sounds present at admission, clinical signs of peritonitis, onset of abdominal symptoms, preoperative severe sepsis [systemic inflammatory response syndrome (SIRS) + source of infection + organ dysfunction/hypotension or hypoperfusion (lactic acidosis, systolic blood pressure <90 mmHg or systolic blood pressure drop ≥40 mmHg)], and American Society of Anesthesiologists (ASA) score. Intraoperative variables collected included the following: type of surgical procedure performed, length of bowel necrosis, location of necrosis, amount of blood loss, and operation time. Postoperative parameters collected included the following: in-hospital survival, histology, surgical site and systemic complications, intensive care unit length of stay (ICU-LOS), and hospital length of stay (HLOS).

Continuous and categorical variables are reported as mean±standard deviation (SD), median±range, and percentages. The highest lactate and pH levels measured within the last 24 h prior to surgery were correlated to the length of necrotic bowel by linear regression analysis. Mean lactate and pH, stratified according to the time before surgery, were compared using analysis of variance (ANOVA). In order to identify risk factors for fatal outcome in patients with AMI, all parameters were compared between the survivor and non-survivor groups. Proportions and continuous variables were compared using the Fisher exact and the Mann-Whitney U

tests, respectively. Potential risk factors were identified using $p<0.2$. Moreover, those variables of special interest were forced into the equation. Forward logistic regression analysis was used to identify independent risk factors for mortality.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Windows©), version 17.0 (SPSS Inc., Chicago, IL). $p<0.05$ was considered statistically significant.

Results

Patient Characteristics

Between March 2006 and December 2012, a total of 91 patients with AMI were identified and included in this study. Demographic characteristics are listed in Table 1. The average age was 66.7±.15.7 years old and 58.0 % ($n=49$) of patients were female. On average, 30.8 % ($n=28$) of patients were on regular therapy with acetylsalicylic acid, 14.3 % ($n=13$) were prescribed phenprocoumon, 9.9 % ($n=9$) clopidogrel, and 54.9 % ($n=50$) at least one antihypertensive drug. A total of 46.2 % ($n=42$) of patients were smokers and 18.7 % ($n=17$) had a history of alcohol abuse. Comorbidities were frequently detected, with 68.1 % ($n=62$) of patients with known cardiovascular disease and 39.6 % ($n=36$) with manifest arteriosclerosis. Furthermore, 42.9 % ($n=39$) had a pre-existing pulmonary disease and 19.8 % ($n=18$) suffered from diabetes mellitus.

Overall, 24.2 % ($n=20$) of patients presented with severe sepsis on admission to our service. On clinical examination, 40.7 % ($n=37$) of patients presented with signs of peritonitis; however, no statistically significant differences between the survivor and the non-survivor groups were found with respect to these two parameters. Of the study population, 82.6 % ($n=78$) underwent an i.v. contrast-enhanced computed tomography (CT) scan before laparotomy, which revealed signs of AMI in 25.3 % ($n=23$) of patients.

Serial Serum Lactate and pH Values

A total of 209 preoperative lactate measurements were available for analysis (2.3±1.1 preoperative lactate values per patient). The highest serum lactate value measured within 24 h before surgery in individual patients showed a moderate correlation, but no statistical significance with the length of bowel necrosis ($r^2=0.257, p=0.058$).

A significant increase in the mean serum lactate levels (4.9±4.2 vs. 3.2±3.1 mmol/L, $p=0.006$) and a decrease in the mean serum pH (7.2±0.1 vs. 7.4±0.1, $p=0.001$) was detected in the period 0 to 6 h before surgery, compared to values >6 h prior to surgery (Fig. 1). This finding was accentuated for patients with >50 cm of necrotic bowel (Table 2). Furthermore, within 24 h before surgery, the non-survivors

Table 1 Demographics and patients characteristics

	All (n=91)	Survivor (n=52)	Non-survivor (n=39)	p
Age (years)	66.9±15.7	65.3±16.4	68.0±15.1	0.209
Gender (male)	42 (46.2 %)	21 (53.8 %)	21 (40.4 %)	0.212
BMI	76 (26.2±5.4)	46 (26.0±5.2)	30 (26.5±5.9)	0.815
Smoking	42 (46.2 %)	27 (51.9 %)	15 (38.5 %)	0.288
Alcohol	17 (18.7 %)	11 (21.2 %)	6 (15.4 %)	0.591
Aspirin	28 (30.8 %)	16 (30.8 %)	12 (30.8 %)	1.000
Phenprocoumon	13 (14.3 %)	9 (17.3 %)	4 (10.3 %)	0.383
Clopidogrel	9 (9.9 %)	6 (11.5 %)	3 (7.7 %)	0.727
Statin	24 (26.4 %)	13 (25.0 %)	11 (28.2 %)	0.812
Antihypertensives	50 (54.9 %)	30 (57.7 %)	20 (51.3 %)	0.671
Arteriosclerosis	36 (39.6 %)	23 (44.2 %)	13 (33.3 %)	0.387
Cardiovascular disease	62 (68.1 %)	36 (69.1 %)	26 (66.7 %)	0.823
Pulmonary disease	39 (42.9 %)	19 (36.5 %)	20 (51.3 %)	0.201
Nephrological diseases	43 (47.3 %)	22 (42.3 %)	21 (53.8 %)	0.297
Diabetes mellitus	18 (19.8 %)	7 (13.5 %)	11 (28.2 %)	0.111
Hepatological diseases	11 (12.1 %)	5 (9.6 %)	6 (15.4 %)	0.520
History of prior surgery	71 (78.0 %)	45 (86.5 %)	26 (66.7 %)	0.039
Patient presented with severe sepsis	20 (22.0 %)	10 (19.2 %)	10 (26.5 %)	0.610
ASA score	3.7±0.7	3.5±0.7	4.0±0.7	0.003
Clinical signs of bowel movement	59 (64.8 %)	36 (69.2 %)	23 (59.0 %)	0.377
CT with signs of ischemia/thrombus	23 (25.3 %)	10 (19.2 %)	13 (33.3 %)	0.148

BMI body mass index, *ASA* American Society of Anesthesiologists, *CT* computed tomography

had statistically higher mean serum lactate values than the survivors (5.6±4.8 vs. 3.0±2.2 mmol/L, $p=0.024$).

A total of 34 patients (37.4 %) had at least two serum lactate measurements within 24 h before surgery. Of those, 17 patients had an increase, and 17 patients a decrease in serum lactate before laparotomy. In this subgroup of patients, an increase in serum lactate did not correlate with the length of bowel necrosis or with outcome. Serial serum C-reactive

protein (CRP) and white cell counts were of no predictive value for any of the outcome parameters (data not shown).

Intraoperative Parameters and Outcome

In all of the 91 patients, an explorative laparotomy was conducted and AMI was confirmed macroscopically and histologically. Bowel ischemia involved the small bowel in

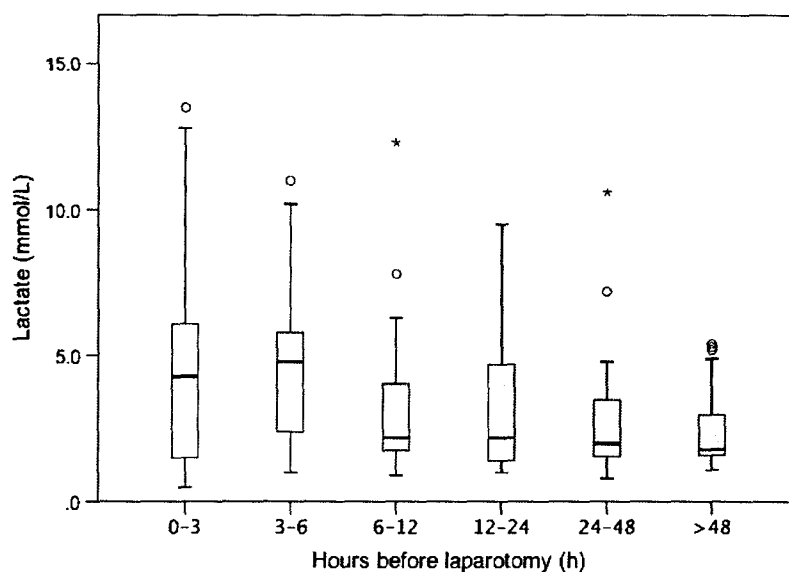**Fig. 1** Serum lactate measurements before laparotomy

Table 2 Correlation of length of bowel necrosis and serum lactate levels

Length of bowel necrosis (cm)	Number	Highest lactate 0–6 h before surgery (mmol/L)	Highest lactate 6–24 h before surgery (mmol/L)	p
<50	40	3.95±2.94 (n=20)	3.19±2.75 (n=9)	0.517
>50	42	6.30±5.36 (n=20)	2.58±1.74 (n=11)	0.034
p		0.094	0.553	

56.1 %, the large bowel in 18.7 %, and both the large and small bowels in 27.5 % of patients. The average length of necrosis was 94.1±103.9 cm.

The in-hospital mortality rate was 42.9 % (n=39). A significantly higher ASA score was detected for the non-survivors than for the survivors (4.0±0.7 vs. 3.5±0.7, p= 0.003). Moreover, the operation time was significantly shorter in the non-survivor group (184±82 vs. 134±89 min, p=0.005). Furthermore, the non-survivors tended to have less intraoperative blood loss than the survivors (454± 657 vs. 273±426 mL, p=0.053).

Ischemia of the small and large bowels combined was significantly more common in non-survivors than in survivors (46.3 vs. 13.5 %; p=0.001). Forward logistic regression showed that the length of necrotic bowel and the highest lactate value within 24 h prior to surgery were independent risk factors for mortality (r^2=0.329).

Discussion

Serum lactate levels are considered an aid in detecting AMI.[9,10] Unfortunately, newer studies have failed to confirm that lactate is a reliable marker and no other reliable serum markers have been identified.[11–13] However, only single preoperative values have been assessed. There have been no studies with serial measurements of lactic acidosis in this group of severely ill patients.

In this study, for the first time, patients with AMI were retrospectively evaluated with the aim to assess the diagnostic role of repeated preoperative serum lactate and pH measurements and to identify risk factors for a lethal outcome in patients with AMI. The 91 study patients were relatively old (66.9± 15.7) and had a high rate of known cardiovascular disease (68.1 %), which is in accordance with the literature and the evolution of the disease—with arteriosclerosis as one of the underlying pathophysiological conditions.[9–14] Among the preoperative parameters obtained, only the ASA score showed a significant difference between the survivor and non-survivor groups, being significantly higher in the non-survivor group (3.47±0.67 vs. 3.97±0.72, p=0.003). However, this finding is most probably not due to the patient's demographics, but rather with the advanced clinical stage of AMI when they presented.

As expected, a high percentage (82.6 %) of patients was evaluated with a CT scan before laparotomy. However, only 25.3 % revealed clear signs of AMI. For the remaining patients, only suspicious signs of AMI were noted within the radiology reports. Different etiologies for bowel necrosis may be the reason for this finding.

All of the 91 patients underwent laparotomy and AMI was confirmed macroscopically and histologically. The mortality rate was 42.9 %. The forward logistic regression analysis revealed that the length of necrotic bowel and the highest lactate value within 24 h prior to surgery were independent risk factors for mortality (r^2=0.329). On average, 94.1±103.9 cm of ischemic bowel was detected. In 56.1 % of patients, solely, the small bowel was affected, which reflects occlusions of the superior mesenteric artery, described as the most frequent site causing AMI.[1] Interestingly, patients with small and large bowel ischemia showed a significantly higher mortality rate (46.2 vs. 13.5 %, p=0.001) than patients with only the small or large bowel affected. This subgroup of patients with small- and large-bowel ischemia could have suffered from multiple thromboembolic events.

Operative time was significantly shorter and intraoperative blood loss was less in the non-survivor group (Table 3). This

Table 3 Intraoperative parameters and outcomes

	All (n=91)	Survivor (n=52)	Non-survivor (n=39)	p
Ischemia >100 cm	23 (29.9 %)	10 (22.2 %)	13 (39.4 %)	0.136
Ischemia >50 cm	39 (50.6 %)	19 (43.2 %	20 (60.6 %)	0.169
Blood loss (mL)	376±500	454±657	273±426	0.053
Operative time (min)	163±88.9	184±82	134±89	0.005
Large-bowel ischemia	17 (18.7 %)	13 (25.0 %)	4 (10.3 %)	0.104
Small-bowel ischemia	51 (56.1 %)	33 (63.5 %)	18 (46.2 %)	0.135
Large- and small-bowel ischemia	25 (27.5 %)	7 (13.5 %)	18 (46.2 %)	0.001
Second look laparotomy	23 (25.3 %)	11 (21.2 %)	12 (13.2 %)	0.336
Length of bowel necrosis (cm)	94.1±104.0	70.6±76.9	127.1±127.3	0.192

finding is explained by the explorative laparotomies without further surgical intervention conducted in patients with generalized, fatal visceral ischemia.

In the current study, more than two serum lactate measurements were available per patient, allowing the detection of an increase or decrease in preoperative values. Interestingly, the overall mean serum lactate level at 0–6 h before surgery was significantly higher and the pH lower than in the period of more than 6 h before surgery. Moreover, the highest serum lactate value measured within 24 h before surgery in individual patients showed a moderate correlation, but no statistical significance with the length of bowel necrosis ($r^2=0.257$, $p=0.058$). However, high variability was observed, and therefore, this finding cannot be translated to the individual patient. To further elucidate the role of serial measurements and to limit the heterogeneity of the measurements, we assessed the subgroup of patients with two or more repeated serum lactate measurements performed within the last 24 h prior to surgery. In this subgroup of 34 patients, 17 had a decrease and 17 an increase in serum lactate before laparotomy, which implies that lactate levels are probably influenced by multiple variables. One of the most important variables might be aggressive fluid resuscitation in deteriorating patients before surgery, as this causes a decrease in lactate values.

The observation that serum lactate might have a predictive value in the amount of bowel affected by ischemia was more robust. In the subgroup of patients with >50 cm of necrotic bowel, a significant increase was found in serum lactate 0–6 h before surgery compared to 6–24 h before surgery. This observation was not statistically significant in those patients with <50 cm of necrotic bowel. Moreover, a trend towards higher serum lactate 0–6 h before surgery was seen in patients with >50 cm ischemia compared to patients with <50 cm ischemia. Once again, these results were highly variable and the number of patients was limited, so that diagnostic interpretation or cutoff analysis is impossible.[15]

The limitations of this study are its retrospective design and the relatively small number of patients, especially of those patients with ≥2 lactate measurements within 24 h prior to surgery. The measurements of lactacidosis were at the discretion of the attending physician causing a wide variability of the timing of the blood tests. Furthermore, the retrospective nature of this study and limited number of patients did not allow to accurately differentiate between the causes of bowel necrosis or a comparison between subgroups. Therefore, the conclusions were drawn with caution.

Conclusion

AMI remains a serious surgical emergency with high mortality. The length of necrotic bowel and the highest lactate

value within 24 h prior to surgery are independent risk factors for mortality. However, serum lactate and pH are of limited value, even when measured repeatedly, as multiple variables probably influence the level of lactacidosis in this group of severely ill patients. To the best of our knowledge, the evaluation of serial serum lactate levels is new to the literature. In this cohort, the serial lactate measurements added no benefits in the evaluation of severely ill patients with AMI.

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