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Endovascular Interventions in Acute Mesenteric Ischemia: The Implication of Lactic Acidosis

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Abstract

Background: In the setting of acute mesenteric ischemia (AMI), lactic acidosis has been used as a surrogate for at-risk or necrotic bowel. The role of endovascular therapy in maximizing outcomes in AMI patients remains controversial and there are no set guidelines for using endovascular intervention as an initial treatment strategy. We sought to determine if the endovascular strategy was safe and effective in patients with AMI who develop lactic acidosis.

Methods and Findings: The Nationwide Inpatient Sample (NIS) was examined for patients presenting with AMI (557.9) between the years 2005-2009. Patients were included if they presented as urgent/emergent and underwent endovascular therapy. Patients were divided according to the presence of lactic acidosis. The primary outcome measured was in-hospital mortality. 663 patients met inclusion criteria. Of these patients, 74 (11.2%) developed lactic acidosis. Patients with lactic acidosis were found to have an increased mortality compared to patients without lactic acidosis when undergoing endovascular treatment (47.1% vs. 20.8%, p = 0.029). The two groups did not differ in rates of bowel resection (19.8 vs. 12.4%, p = 0.41), TPN administration (23.1% vs. 14.1%, p=0.382) or length of stay (11.4 days vs. 13.6 days, p=0.54). The main limitation of this study was the use of a large database that precluded granular level data regarding patient characteristics and decisions for management strategies.

Conclusions: Endovascular intervention should be considered cautiously as a primary therapeutic strategy in AMI patients with lactic acidosis as it was associated with increased mortality. The presence of lactic acidosis in patients with AMI was not associated with worse bowel related outcomes and thus may not be useful to determine whether open surgery is mandated as an initial approach.

Keywords: Acute mesenteric ischemia; Endovascular repair; Lactic acidosis; Outcomes

Introduction

Acute mesenteric ischemia (AMI) represents one of the deadliest vascular insults surgeons encounter. The reported incidence of AMI is low, representing only 0.1-0.2% of all hospitalizations in the United States [1]. Its mortality rate, however, is alarmingly high, with many recent reports citing between 24-81% [2-4]. Further, the rate of mortality demonstrates a time-dependent increase, with delays in diagnosis greater than 24 hours resulting in an increase to more than 70% [5]. In the era of rapid computed tomography, some of this delay may be abated by recognition of radiographic signs of vascular occlusion, including pneumatosis, bowel edema, and solid organ malperfusion. The recognition of radiographic signs of a possible vascular catastrophe, such as pneumatosis, bowel edema, portal venous gas, and solid organ injury, could result in a dramatic decrease in the delay to diagnosis and intervention [6]. While serum lactate has been proposed as

a possible marker of bowel ischemia, its utility as a predictor of lactic acidosis is poor (sensitivity and specificity, 66% and 53%, respectively) [7]. Indeed, it may be an inaccurate measure of irreversible bowel ischemia in patients with symptoms and radiographic findings consistent with AMI.

The use of endovascular therapy for the treatment of AMI has increased in the past decade. While open surgical revascularization remains the preferred treatment modality in the United States, rates of endovascular therapy have surpassed open revascularization for the treatment of AMI in Europe [8,9]. As with most vascular crises, patient selection is crucial in determining the appropriate method of intervention, whether it be endovascular or open [10]. Endovascular therapy, primarily by the administration of catheter-directed thrombolysis, has a high technical success rate and may be associated with decreased rates of pulmonary and renal consequences [11]. Due to a concern regarding the integrity of the bowel in question, however, many surgeons may be driven to an open approach to revascularization, which allows for concurrent interrogation of bowel integrity. Currently, mortality rates are nearly equivalent between the two therapies with the decision to proceed with either largely dependent on the operator [12]. Unfortunately, no guidelines exist as to the use of specific laboratory values or CT findings to direct initial therapy toward the less invasive approach.

Accordingly, we sought to evaluate outcomes amongst AMI patients undergoing endovascular therapy who developed lactic acidosis to identify if the endovascular approach in these patients was still associated with good outcomes.

Methods

Our Institutional Review Board approved this study. The Nationwide Inpatient Sample (NIS) was queried between 2005 to 2009 for patients presenting with acute mesenteric ischemia using ICD-9 code 557.0 Patients were included if their admission status was listed as urgent or emergent. ICD-9 codes corresponding to insertion of non-drug-eluting intra-arterial stents into intra-abdominal arteries (39.90) or injection or infusion of thrombolytic substance (99.10) were used to identify patients who had undergone endovascular repair. Patients were then stratified according to the presence of lactic acidosis at admission using ICD-9 code 276.2. Patient-specific variables such as age, gender, and comorbid conditions were collected: the latter included hypertension, hyperlipidemia, cardiovascular disease, peripheral vascular disease, cerebrovascular disease, renal dysfunction, congestive heart failure and obstructive pulmonary disease. The presence of hypotension (458.9), systemic inflammatory response syndrome (SIRS, 995.91) and acute respiratory distress syndrome (ARDS, 518.5) were used as surrogates for the acuity of disease at presentation, as previously reported [13]. In-hospital mortality was the primary outcome of interest. Secondary outcomes included the need for subsequent bowel resection, usage of total parenteral nutrition, and length of stay.

Statistical analysis

Chi-squared analysis was performed for categorical and dichotomous variables. Wilcoxon rank-sum test was used to examine the difference between the medians of the continuous

Table 1 Demographics for patient cohorts with and without lactic acidosis. SE: Standard Error; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; CVD: Cerebrovascular Disease; PVD: Peripheral Vascular Disease; COPD: Chronic Obstructive Pulmonary Disease; SIRS: Systemic Inflammatory Response Syndrome; ARDS: Acute Respiratory Distress Syndrome.

Variables	Lactic Acidosis		
	NO n(%)	YES n(%)	P
Total Population (row %)	589 (88.8)	74 (11.2)	-
Mean age (SE)	62.7 (1.67)	71.8 (3.83)	0.070
Female	312 (53.0)	39 (52.4)	0.969
Admission type			0.902
Emergency	448 (75.6)	57 (77.0)	
Urgent	144 (24.4)	17 (23)	
Comorbidities			
Hypertension	240 (40.7)	23 (31.5)	0.517
Hyperlipidemia	43 (7.3)	17 (22.3)	0.057
CAD	124 (21.1)	29 (39.2)	0.138
CHF	49 (11.0)	15 (26.7)	0.133
CVD	27 (4.6)	0 (0)	-
PVD	45 (7.7)	7 (10.0)	0.796
COPD	117 (26.4)	5 (8.8)	0.206
Renal disease	44 (10.0)	5 (9.3)	0.945
Measures of acute illness severity			
Hypotension	19 (4.3)	5 (9.3)	0.469
SIRS	20 (4.5)	10 (17.2)	0.092
ARDS	20 (4.6)	15 (25.7)	0.009

Table 2 Primary and secondary outcomes among cohorts, a: column percentages unless otherwise indicated next to the variable name. TPN: Total Parenteral Nutrition; LOS: Length of Stay.

Outcomes	Lactic acidosis		
	No n (%)[a]	Yes n (%)[a]	P
Mortality	123 (20.8)	35 (47.1)	0.029
Bowel resection	73 (12.4)	15 (19.8)	0.407
TPN	83 (14.1)	17 (23.1)	0.382
Mean LOS (SE)	13.6 (1.08)	11.4 (2.48)	0.540

variables collected. Significance was established at a p-value of less than 0.05.

Results

Demographics

Between the queried years, 663 patients met inclusion criteria for presenting with acute mesenteric ischemia and undergoing endovascular repair. By design of the study, all patients were admitted urgently or emergently. Lactic acidosis developed in 74 (11.2%) of patients. The mean age at presentation and gender status did not differ significantly between the two cohorts. The groups were also largely similar in the presence of comorbid conditions (**Table 1**). When comparing measures of acute severity of illness, patients in the two cohorts demonstrated similar rates of hypotension and SIRS while there was a significantly higher rate of ARDS among the cohort of patients presenting with lactic acidosis.

Outcomes

Despite a significantly shorter time-to-intervention after admission to the hospital for patients who developed lactic acidosis (0.3 vs. 2.2 days, p<0.001), there was a statistically significant higher rate of in-hospital mortality (47.1 vs. 20.8%, p=0.03). Lactic acidosis in patients undergoing endovascular treatment was not associated with an increased rate of bowel resection, TPN administration or length of stay between the two groups (**Table 2**).

Discussion

Improved survival in acute mesenteric ischemia relies on early and accurate diagnosis and the choice of an appropriate intervention. Relying solely on the subtle signs of a physical exam can have disastrous consequences as the findings are almost always non-descript [14]. The application of serum lactate levels as a biomarker for bowel malperfusion has been proposed as a tool to aid in early diagnosis, but due to differences in hepatic clearance amongst patients, its utility has been questioned [15]. Furthermore, while the predictive capacity of lactate to determine cases of unsalvageable necrosis is acceptable, its ability to discern reversible ischemia is unknown [7]. The latter being especially important when considering the suitability of endovascular procedures where in dead bowel is left intra-abdominal among staged approaches, such as thrombolysis.

While the use of endovascular approaches in treatment of AMI is increasing, many practitioners may be driven to an open procedure due to the ability to assess bowel viability at the time of the operation [8,9]. Indeed, mesenteric ischemia is associated with a 53% rate of bowel resection when including repairs with both open and endovascular procedures, and a 48% rate among second-look laparotomies [14]. Even after technically successful endovascular repair, there may be as high as a 70% rate of laparotomy to assess bowel viability [11]. In our analysis, there were no differences in the rates of bowel-related outcomes, including bowel resection, among patients who developed lactic acidosis and underwent primary endovascular repair (12.4 vs. 19.8%, p=0.41). In turn, these results would seem to question the use of lactate as a marker of irreversible bowel ischemia and as a motivator of clinical decision making toward initial open surgery. With recent reports of improved mortality among patients undergoing endovascular repair for AMI, some authors have purported the benefit of an "endovascular first" strategy in which second-look laparoscopy is performed 24-48 hours following the initial repair [10,12,14,16]. Importantly, our results suggest caution to any strategy for patients with lactic acidosis, as mortality was significantly increased. Whether an "endovascular first" strategy in patients without lactic acidosis represents the ideal indication will require further study, utilizing very specific patient-level data that is not afforded in our analysis (degree of academia, onset of pain, for example). Nonetheless, our results may suggest, given the time to intervention in our study of 0-2.2 days, those patients without lactic acidosis and an explicit history of symptomatology limited to less than 48 hours may be ideal candidates for an endovascular first approach, possibly helping to reduce the higher rates of mortality previously reported to be associated with open repair (24.9 endovascular vs. 39.3% open) [10].

Our analysis demonstrated that the cohort with lactic acidosis experienced a higher mortality despite a shorter time to intervention after hospitalization. Important to consider, pre-hospitalization morbidity and time delays to presentation are unfortunately common in this population and our dataset does not allow for meaningful assessment of pre-hospitalization illness and degree of lactic acidemia. In effect, this may result in a time bias inherent to the data. Previous studies have reported a significant improvement in survival in patients undergoing intervention in less than 12 hours from presentation [17]. These findings may help to further highlight our association between lactate and mortality among patients undergoing endovascular therapy. Interestingly, in our evaluation, increased mortality did not correlate with an increased rate of bowel resection. Although the exact mediator for this increased mortality remains unknown, it is possible that the profound metabolic disturbance associated with even transient ischemia plays a pivotal role. Further, the finding of a higher incidence of ARDS in the lactic acidosis cohort would suggest a multi-factorial mechanism for the death of such patients, and bowel injury may not be the main driver of patient mortality. We also demonstrated a 20.8% rate of mortality in the patients who underwent endovascular repair without lactic acidosis at the time of presentation. This is far lower than the commonly reported rate of mortality for all patients with AMI approximating 70% [14]. Indeed, this suggests the absence of lactic acidemia may help identify a patient population particularly suited for endovascular repair, though further studies are needed to truly clarify this population, especially in comparison to open

revascularization. Again, patient-level characteristics beyond those captured in NIS would be required to state definitively the primary treatment strategy.

There remain significant challenges in the diagnosis and treatment of AMI. Chiefly, the determination of an open or endovascular treatment paradigm may be largely driven by clinical examination and intuition, as lactic acidosis is only one of the possible predictors of outcomes after either approach. Indeed, our study was not designed to determine the effect of lactic acidosis on open versus endovascular treatment, which limits the ability to make conclusions regarding the outcome of patients with lactic acidosis who undergo open repair. Furthermore, even in open surgery, the assessment of bowel viability is not easily discerned. In standard practice, the surgeon utilizes sodium fluorescein injection after revascularization to determine resection margins. A more bowel-specific biomarker or radiologic test of mucosal injury would be of benefit, especially in an "endovascular first" paradigm. While lactic acidosis remains the only easily drawn serum test to suggest malperfusion, it may be insensitive to follow patients as an indicator of treatment success. For example, in ischemic colitis associated with ruptured abdominal aortic aneurysm, Champagne et al. demonstrated that a lactate within the normal reference range did not rule out the presence of bowel with significant ischemia as determined by colonoscopy [18]. Nonetheless, the development of lactic acidosis in patients treated with an endovascular approach should not be diminished and, in current practice, is the only potential indicator of treatment failure.

There are limitations to this study. First, the NIS is built based on billing codes and as such, may not accurately capture all disease-related specifics that could impact mortality. Most limiting when using this database, lactic acidosis is coded as a categorical variable rather than a continuous one: we cannot stratify outcomes based on lactate levels and this precludes the determination of what exact serum lactate level should specifically guide treatment or is associated with clear treatment failure. Further, within the variables reported to NIS, there is a limited ability to predict the acute severity of illness that may drive a practitioner to a certain intervention. We have attempted to mitigate these limitations by including three variables (hypotension, SIRS, and ARDS) to identify more critically "ill" patients, as previously published [13]. Among these, we demonstrated no difference in the rates of SIRS and hypotension between the two cohorts. ARDS, however, appears to occur more often in patients with lactic acidosis and may independently impact their survival. However, given the lack of data concerning the timing for development of ARDS, it is difficult to tell if patients with ARDS were more likely to have lactic acidosis given the derangement of their ability to establish respiratory compensation for their metabolic derangement. Further, the strategy of limiting fluids in patients with ARDS may have contributed to the development of lactic acidosis, though there are not decision-level data to confirm this hypothesis. Finally, the limited number of total patients identified during this time period impacted our ability to detect small differences between the two groups.

Conclusions

As endovascular intervention for AMI in patients who developed lactic acidosis was associated with significantly increased mortality, endovascular interventions should be considered cautiously as a primary therapeutic strategy in this setting. However, the presence of lactic acidosis in patients with AMI was not associated with worse bowel related outcomes and thus may not be useful to determine if open surgery is mandated as an initial approach for AMI over endovascular strategies.

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