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Initial Venous Lactate Levels in Patients with Isolated Penetrating Extremity Trauma: A Retrospective Cohort Study

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Abstract

INTRODUCTION—Elevated initial lactate levels have been shown to be associated with severe injury in trauma patients, but some patients who do not appear to be in shock also present with elevated lactate levels. We hypothesized that in hemodynamically stable patients with isolated penetrating extremity trauma, initial lactate level does not predict clinically significant bleeding.

METHODS—A 5-year institutional database review was performed. Hemodynamically stable patients (HR<101, SBP>90) with isolated penetrating extremity trauma with an initial lactate sent were included. The exposure of interest was captured as a dichotomous variable by initial lactate level Normal (N 2.2 mEq/l), Elevated (E >2.2. mEq/l). The primary outcome measurement was clinically significant bleeding, defined by need for intervention (operation, angioembolization, or transfusion) or laboratory evidence of bleeding (presenting Hg<7g/dL, or Hg decrease by >2g/dL/24hours). Chi-squared and Mann-Whitney tests were used to compare variables.

RESULTS—A total of 132 patients were identified. There were no differences in demographics or mechanism of injury between the N (n=43, 7%) and E (n=89, 14%) groups. Median lactate levels were 1.6 (IQR 1.2–1.9) mEq/dL vs. 3.8 (IQR 2.8–5.2) in the N and E groups, p<0.001. Lactate was elevated in 89 (67%) patients but was not associated with clinically significant bleeding (37% elevated vs. 39% not elevated p=0.82).

CONCLUSIONS—In hemodynamically stable patients with isolated penetrating trauma to the extremity, elevated initial venous lactate levels (>2.2mEq/l) are not associated with bleeding or

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Conflict of interest statement:

Ian W Folkert, Carrie A Sims, Jose L Pascual, Steven R Allen, Patrick K Kim, C. William Schwab, and Daniel N Holena declare that they have no conflict of interest.

Ethical Standards Statement

This study was approved by the Institutional Review Board of the University of Pennsylvania and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

need for interventions. Clinical judgment remains the gold standard for evaluation and management of these patients.

Introduction

Venous lactate levels have been studied extensively in critically ill patients as a predictor of multi-organ failure and death [1–4]. Lactic acid is produced as a result of anaerobic metabolism and is therefore often considered to reflect a state of inadequate tissue perfusion. Hemorrhage is the most common cause of shock in trauma patients, and in mixed cohorts elevated lactate levels on admission have been shown to be associated with mortality and severity of injury [5–10].

As with any clinical test, the predictive ability of venous lactate levels depends in part upon the population in which it is used. Some trauma patients who present with elevated lactate levels do not appear to be in a state of overt shock. The presence of an elevated lactate in the absence of other clinical indicators suggesting a state of shock may lead to the diagnosis of an of ‘occult’ shock state with measures taken to treat accordingly [11]. Observationally, we noted that many hemodynamically stable victims of penetrating trauma often exhibited elevated lactate levels on initial laboratory studies, even with injuries that appeared to be minor and in the absence of a history of significant bleeding. Given the established relationship between elevated lactate levels and mortality in severely injured trauma patients, this finding sometimes leads to changes in management including administration of additional resuscitation, increased diagnostic testing, and prolonged periods of observation when clinical judgment alone might suggest these measures are unnecessary.

In this retrospective cohort study, we examined initial venous lactate levels in a cohort of hemodynamically stable patients with isolated penetrating extremity injuries. We hypothesized that in this subset of trauma patients, initial lactate levels are frequently elevated but are not a marker of an occult shock state secondary to hemorrhage. Because of the inherent difficulties in trying to measure a state which is by definition not able to be observed, we chose to measure a clinically relevant surrogate of occult hemorrhagic shock consisting of a combination of the need for intervention to control hemorrhage or evidence of bleeding. We hypothesized that there would be no difference in rates of this endpoint between those patients presenting with elevated lactate levels and those without.

Methods

This retrospective review was conducted in accordance with the ethical standards of the Perelman School of Medicine at the University of Pennsylvania and was approved by the Institutional Review Board.

The Hospital of the University of Pennsylvania is an academic level 1 trauma center located in urban Philadelphia. We performed a 5-year query of our institutional trauma registry from 1 January 2006 to 31 December 2010. The data for this registry is prospectively collected by trained nurse abstractors as part of the Pennsylvania Trauma Outcomes Study (PTOS). Demographic data, presenting vital signs, mechanism of injury, and need for surgical or angiographic intervention to control bleeding were abstracted from our institutional PTOS

database. Laboratory values, toxicology reports, and transfusion requirements were abstracted from the electronic medical record.

Patients were included if they were hemodynamically stable on presentation to the trauma bay (initial HR<101, SBP>90), had sustained isolated penetrating trauma to the extremities, and had a venous lactate level sent during their initial evaluation. Patients who had injuries in body regions other than the extremities, those less than 16 years of age, pregnant, or prisoners were excluded. Patients were divided into groups based on the primary exposure of interest- elevated initial venous lactate level (as defined by a serum Lactic Acid level of >2.2mmol/L, which is the upper limit of normal used by the laboratory at our institution). The primary outcome measurement was a combined surrogate endpoint of evidence of clinically significant bleeding, either on arrival to the trauma center or in the pre-hospital setting. Clinically significant bleeding on arrival to the trauma bay was defined as the need for packed red blood cell transfusion or intervention (surgery or angioembolization) to control bleeding. Significant pre-hospital bleeding was defined as a presenting hemoglobin of <7g/dL or a decrease in hemoglobin ≥ 2 g/dL/24hours, in order to capture patients who may have bled in the field but had not yet equilibrated hemoglobin levels by the time they arrived at the trauma center.

All lactate levels were obtained from venous lactate samples, which were drawn on admission and sent immediately to a central processing laboratory for rapid analysis. Samples were processed by our laboratory using the UniCel DxH 600/800 analyzer, with a clinically reportable range of 0.3–22.0 mmol/L and a reference range of 0.5–2.2 mmol/L. These reference ranges were determined by the manufacturer of this assay system and subsequently validated by independent in-house testing. Because of the reported association between common intoxicants such as alcohol [12–15] and cocaine [16, 17] and elevated lactate levels we also explored the association between common intoxicants (ethanol, cocaine, amphetamine, barbiturates, opiates, phenylcyclidine, benzodiazepines, and tetrahydocannabinol) and lactate levels using the results of serum ethanol levels and urine toxicology reports in the subset of patients for whom they were available.

Univariate statistical testing was performed using chi-squared or Fischer's exact test for categorical variables, as appropriate. Nonparametric continuous variables were compared using Mann-Whitney test. The predictive ability of initial serum lactate levels in this cohort was examined using the laboratory-defined cut point of 2.2mmol/L using Receiver Operator Characteristic curve (ROC) analysis. Additionally, ROC analysis was used to determine if a different cut point might be of diagnostic value in this cohort. Area Under the Curves (AUCs) for ROC curves were compared examining the predictive ability of initial lactate levels as a categorical vs. continuous cut point. Two-tailed statistical significance was set at $p=0.05$ and all statistical analysis was performed using Stata IC v12.1 (College Station, TX, USA).

Results

A total of 132 patients meeting inclusion criteria with no exclusion criteria were identified. Patients were 90% male, 89% African American, and had a median age of 25 years (IQR20

- 34 years). Serum lactate levels were elevated in 89 (67%) patients with a median of 2.8 mmol/L (range 0.8–18.4mmol/L) (Figure 1). Patients with elevated lactate levels (n=89, 67%) were not different in terms of demographics or mechanism of injury when compared to patients with normal lactate levels (n=43, 33%). Median lactate levels in those patients with normal (< 2.2mmol/L) and elevated (≥ 2.2mmol/L) initial serum lactate levels were 1.6 (IQR 1.2–1.9) mEq/dL vs. 3.8 (IQR 2.8–5.2) respectively (Table 1).

When the combined endpoint of clinically significant bleeding was examined, there was no significant difference between patients with normal (n=16, 37%) and elevated (n=33, 37%) initial venous lactate levels (Table 2). In analysis of secondary endpoints, neither evidence of pre-hospital hemorrhage (29% vs. 26%, p=0.66) or need for intervention to control hemorrhage (37% vs. 37%, p=0.99) was more common in the group presenting with elevated lactate.

Ethanol was present in the serum in 24 (19%) of the 125 patients in whom serum ethanol levels were checked. When considered as continuous variables using linear regression, there was no association between lactate levels and ethanol levels ($\beta = 0.0021$, 95% CI -0.01–0.01). Evaluation of this relationship with dichotomized variables using laboratory defined cut-points of 2.2mmol/L for elevated lactate and 80mg/dL for ethanol intoxication also demonstrated no association between the two variables (OR for elevated initial lactate given ethanol intoxication 2.01, 95%CI 0.58–8.88).

Urine toxicology was assayed in 36 (27%) of the cohort and was positive for one or more intoxicants in 29 (80%) of cases. The most frequent intoxicants encountered were tetrahydrocannabinol (THC) and cocaine, present in 44% and 30% of patients respectively. The majority of intoxicants tested were present in frequencies too small to allow meaningful statistical evaluation, but we found that cocaine use was not more common in those with elevated lactate levels than without (28% vs. 36%, p=0.6) (Table 3). Of note, however, 15/16 (94%) patients with urinary drug screens positive for THC had elevated initial lactate levels.

In receiver operator characteristic curve analysis, the laboratory-defined cut point for elevated levels of serum lactate 2.2mmol/L had an area under the curve (AUC) of 0.51 (95%CI 0.43–0.59), indicating that the test did not meaningfully alter the pre-test probability of the combined endpoint of clinically significant bleeding. When considered as a continuous variable, the discriminatory utility of serum lactate level remained poor (AUC 0.57 95%CI 0.46–0.67) and was not statistically different from that of the dichotomous cut point (p=0.06) (Figure 2).

Discussion

In this cohort of hemodynamically stable patients with isolated penetrating trauma to the extremities we found that venous lactate levels on admission were elevated nearly two-thirds of the time. This elevation was not associated with the need for transfusion or the need for intervention to control hemorrhage, nor was it associated with evidence of pre-hospital

bleeding. This finding does not support the generally accepted view that elevated lactate levels on presentation represent a state of shock and are associated with negative outcomes.

The putative mechanism for lactate elevation in injured and critically ill patients is anaerobic glycolysis by cells subjected to a state of global hypoperfusion or hypoxia [18, 19]. For this reason, lactate is thought to more closely represent the patient's metabolic processes at the cellular level than the hemodynamic parameters normally used to guide resuscitation. Several studies have suggested that lactate is superior to clinical indicators of adequate tissue perfusion – including heart rate, blood pressure, and urine output—that may not accurately reflect hypoperfusion at the cellular level [7, 3, 20, 21, 10, 22]. Within the population of trauma patients, lactate level has been used as a surrogate of perfusion status, to guide resuscitation, and to predict which patients are likely to have a poor outcome [18, 5, 2, 23, 24]. Cerovic et al. [25] found that there was a strong correlation between initial serum lactate level, severity of injury, and survival in trauma patients. In a subsequent study by Paladino et al. [26], initial serum lactate level was also found to help discriminate between minor or major injury (Injury Severity Score > 15) in trauma patients. In light of these data, recent evidence-based European guidelines for the management of bleeding and coagulopathy following major trauma recommend that serum lactate or base deficit be used to estimate and monitor the extent of bleeding and shock (evidence grade 1B) [27].

There are several possible reasons our results stand in contrast to available evidence supporting lactate as a marker of hypoperfusion and negative outcomes in other studies. Although lactic acidosis may be a result of a shock state, by limiting our analysis to hemodynamically stable patients with isolated penetrating extremity trauma, we have effectively ruled out many of the possible causes of shock after trauma (tension pneumothorax, myocardial injury, spinal cord injury) that might explain the frequent elevations in lactate that we saw. For the same reason, hypoxia as an etiology of this finding is also unlikely. Beyond shock states, there are numerous other potential causes of elevated lactate levels that may render this finding non-specific without further clinical investigation. Other potential causes of lactate elevations include increased levels of circulating catecholamines, anaerobic exercise, and drug or alcohol intoxication. As the patient cohort we studied were all victims of interpersonal violence, it is possible that lactic acidosis may have been related to 'fight or flight' catecholamine surges. In animal models, infusion of epinephrine may lead to elevated lactate levels through stimulation of sodium potassium exchangers in skeletal muscle [28]. Fear is a well-known secretagogue of catecholamines, and fear states in humans such as panic disorder have been demonstrated to be associated with elevations in serum lactate levels [29, 30]. Alternatively, the intense physical activity associated with interpersonal violence (fighting, fleeing) could in and of itself be responsible for elevated initial lactate levels. In a study of law enforcement simulation of "use of force" encounters, Ho et al found that lactic acid levels were elevated in subjects undergoing vigorous physical activity (median lactate level 15.46 mmol/L after heavy bag workout and 10.98 mmol/L after sprinting), and that these levels remained at this level or higher up to 10 minutes post-exercise [31]. Pre-hospital transport times at our center tend to be short (mean of 19 minutes in a similar setting in the same city [32]) and it is possible that some of the lactic acid elevations observed may have been secondary to recent intense physical activity related to attempting to avoid injury.

Other investigators have reported relationships between alcohol [16, 14, 12, 13] and cocaine intoxication [16, 17] and elevated initial lactate levels. Although these findings were not replicated in the current study, we did find a very strong relationship between THC use and elevated lactate levels with 15/16 (OR 15 95%CI 1.56– 693.14) patients who screened positive for THC having an elevated initial lactate level. Data regarding serum lactate levels after cannabis utilization in both human and animal studies are scarce and contradictory. A single human subjects study from 1974 demonstrated a decrease in serum lactate levels immediately after smoking cannabis [33], but administration of THC in canine models has been shown to result in increased peripheral vascular resistance and serum lactate levels [34]. The mechanism and significance of this finding are unclear but this relationship warrants further investigation. Because we do not have complete toxicology reports for all patients in this study, we are not able to say what proportion of elevated lactate levels could be due to this factor. Positive urinary drug screens were found in 80% of the subset of patients in which they were checked, but this number must be interpreted with caution. First, opiates and benzodiazepines are included in the urinary drug screen but because these medications are commonly used in the care of trauma patients, some portion of the positive results could be secondary to administration of these agents after arrival at the trauma center. Excluding positive tests for opioids and benzodiazepines still results in 66% urine drug screen positivity rate, but because clinical judgment is used to decide who undergoes screening, the rate of positive tests is expected to be higher in patients who appear intoxicated. Therefore, this rate is also likely to overstate the prevalence of use of intoxicants in the overall cohort.

Whatever the reason for the frequent elevations in initial serum lactates we observed, ROC curve analysis demonstrates that initial lactate levels have essentially no predictive power to discriminate between patients who do and do not have any clinically significant blood loss in this population. This was true whether lactate was used as a dichotomous variable defined by a standard laboratory cut point of 2.2 mmol/L or as a continuous variable, with no significant differences between the two approaches. Use of lactate levels did not alter the pre-test probability (37%) of meeting the combined endpoint of needing an intervention to control bleeding or evidence of clinically significant bleeding, suggesting the predictive power of this test in this patient population and setting is essentially the equivalent of flipping a coin (AUC~0.50).

This study is a retrospective analysis of a single center experience with the inherent limitations of such a design. Our patient population consists primarily of young African American males, and therefore our data may not be applicable to other centers with varying demographic compositions. Because of our relatively small sample size, the possibility exists that there is a true difference between our two groups but that we lack the statistical power to detect it (type II error). It is notable however that the rates of our combined endpoint of need for intervention or clinically significant bleeding as well as the subcategories which comprise it were strikingly similar between the two groups. Further accrual of patients in this cohort may allow for future reporting with increased statistical power. Finally, our study is focused on a very small subset of the overall trauma population, and cannot (and is not intended to) be generalized to patients who would not have met inclusion and exclusion criteria of the current study.

To our knowledge, this is the first study specifically examining the utility of initial venous lactate in hemodynamically stable patients with isolated penetrating injuries to the extremities. Our results suggest that in hemodynamically stable patients with isolated penetrating injuries to the extremities, elevated initial venous lactate levels do not appear to be intrinsically meaningful. Clinicians treating this subset of trauma patients should exercise clinical judgment in determining the treatment course of these patients.

Conclusion

In hemodynamically stable patients with isolated penetrating injuries to the extremities, initial venous lactate levels are frequently elevated ($>2.2\text{mEq/l}$). These initial elevated values, however, have no clinical utility in predicting significant hemorrhage or need for intervention in this subset of patients. Clinical judgment remains the most important factor in determining the need for further intervention in these patients.

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Figure 1. Initial venous lactate levels (mmol/L) in the overall cohort. Vertical line = laboratory defined cut point of elevated (2.2mmol/L).

Figure 2. Receiver Operator Characteristic curve analyses of initial serum lactate level as a categorical value (A - cut point 2.2mmol/L) and continuous variable (B) to predict the clinically significant bleeding.

Table 1

Demographics and mechanisms of injury. Continuous values expressed as median (Interquartile Range); Categorical values expressed as n (%). P values are for Mann-Whitney, chi square, or Fisher's exact test as appropriate.

	Initial Lactate Level		p
	Normal n=43	Elevated n=89	
Initial lactate level (mmol/L)	1.6 (1.2– 1.9)	3.8 (2.8– 5.2)	<0.001
Age in years	28 (20–42)	24 (20–31)	0.1
Male gender	40 (93%)	80 (90%)	0.56
Race			0.15
African American	36 (84%)	82 (92%)	
Caucasian	4 (9%)	6 (7%)	
Other	3 (7%)	1 (1%)	
Mechanism of Injury			0.06
Gunshot wound	27 (63%)	71 (80%)	
Stab	12 (28%)	18 (20%)	
Other	4 (9%)	0 (0%)	

Table 2

Evidence of clinically significant bleeding by group. Abbreviations: Hg = serum Hemoglobin. Continuous values expressed as median (Interquartile Range); Categorical values expressed as n (%).(%).P values are for Mann-Whitney, chi square, or Fisher's exact test as appropriate.

	Initial Lactate Level		p
	Normal n=43	Elevated n=89	
Need for Intervention or Evidence of bleeding	16 (37%)	35 (39%)	0.82
Need for Intervention Operation	14 (32%)	23 (26%)	0.42
	10 (23%)	15 (17%)	
Angioembolization	7 (16%)	16 (18%)	
Transfusion	4 (9%)	10 (11%)	
Evidence of Bleeding	11 (26%)	26 (29%)	0.66
Initial Hg<7g/dL	3 (7%)	1 (1%)	
Hg drop>2g/dL/24 hours	8 (19%)	23 (26%)	

Table 3

Urine toxicology results in the subset of patients in which it was tested (n=36).

	Initial Lactate Level		p
	Normal n=11	Elevated n=25	
Cocaine	4 (36%)	7 (28%)	0.6
Amphetamine	0 (0%)	1 (4%)	0.5
Barbiturates	0 (0%)	0 (0%)	*
Methadone	0 (0%)	1 (4%)	0.5
Opiates	3 (27%)	8 (32%)	0.8
PCP	0 (0%)	2 (8%)	0.3
Benzodiazepines	1 (9%)	10 (40%)	0.06
THC	1 (9%)	15 (60%)	0.005

Abbreviations: PCP = Phencyclidine; THC = Tetrahydrocannabinol. Categorical values expressed as n (%). P values are for Fisher's exact test.