Prehospital Lactate for the Identification of Shock in Trauma

DSMB 08/12/2010
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Summary
Prehospital Lactate for the Identification of Shock in Trauma

Primary Aim: To compare prehospital lactate (P-LAC) levels to systolic blood pressure (SBP) ≤ 90 to predict the need for resuscitative care (the administration of packed red blood cells (PRBCs), emergent intervention for hemorrhage control using thoracotomy, laparotomy, pelvic fixation or interventional radiologic control) or death within 6 hours of ED arrival in patients with 70 < SBP ≤ 100 in the prehospital setting.

Secondary Aim: To evaluate the usefulness of P-LAC, when combined with other prehospital variables (age, heart rate, systolic blood pressure, GCS, mechanism of injury), in predicting the need for resuscitative care.

Primary Null Hypotheses: The null hypotheses are that lactate has the same (under the alternative hypothesis higher) sensitivity (without any concomitant loss of specificity) as SBP ≤ 90 to predict the need for resuscitative care (the administration of PRBCs, emergent intervention for hemorrhage control) or death prior to or within 6 hours of ED arrival in patients with SBP between 70 and 100 (70<SBP≤100) treated by ground or air medical services who have not received lactated ringers prior to lactate measurement.

Secondary Null Hypotheses: The secondary null hypotheses are that there is no association between P-LAC and the need for resuscitative care after taking other pre-hospital covariates into account.

Inclusion Criteria: Patients meeting local trauma triage criteria for traumatic injury, a systolic blood pressure ≤100, placement of an IV, and transported to a level I or II trauma center or died in the field or en route (with SBP≤100 and after placement of an IV).

Exclusion Criteria: Known prisoners, age <15 years, obvious isolated penetrating head injury, hanging, drowning, primary burn related injury, and blunt or penetrating injury with burns >20% of total body surface area.

Design: A prospective observational study. These data will be used to determine the utility of prehospital lactate as a triage tool as well as for identifying patients that may benefit from future ROC interventional trials. No intervention will be performed and pre-hospital providers and clinicians will be blinded to the prehospital lactate results.

Setting: EMS agencies with a limited number of ALS units responding to a high volume of patients with traumatic injury and SBP ≤100 and transporting to a small number of trauma centers to facilitate data collection.

Sample Sizes: a) Air medical services: The study has 90% power to detect a difference in sensitivity of 12.9% if 235 patients with SBP between 70 and 100 are enrolled (two-sided test with alpha=0.025). b) Ground medical services: The study has about 90% power to detect a difference in sensitivity of 10.5% if 360 patients with SBP between 70 and 100 are enrolled (two-sided test with alpha=0.025).

Statistical Analysis: (Primary hypotheses) We will use McNemar’s test comparing sensitivity of SBP ≤ 90 and a lactate cutpoint (with the same specificity as SBP ≤ 90) separately for patients treated by ground and air medical services (two-sided tests with α=0.025 for each test). Other analyses: descriptive statistics for lactate level; baseline and prehospital characteristics will be reported. Multivariable logistic regression and classification and regression tree methodology.
will be used to explore the effect of other factors that might be related to the need for advanced care or might improve identification of patients in need of advanced care.

**Anticipated Significance:** Previous studies have indicated that a prehospital lactate $\geq 2.5$ mmol/L can identify trauma patients at increased risk of death or need for resuscitative resources utilization. If prospectively validated, prehospital lactate might be useful for triage and identification of a patient population suitable for future ROC studies.

**Human Subjects Protection:** We will seek a waiver of informed consent because this is a minimal risk observational study in which a diagnostic test will be performed on a drop of blood obtained from an existing intravenous line.
1. Overview

We will enroll all patients meeting local trauma triage criteria for traumatic mechanism with a systolic blood pressure $\leq 100$, IV access and transport to a level I or II trauma center. Data from this cohort of patients will be used to determine the ability of lactate to predict the need for resuscitative care. Patients who are known prisoners, less than 15 years of age, or obvious isolated head injury will be excluded from the study.

After intravenous line placement but prior to the initiation of any IV fluids, each enrolled patient will have an approximately 5 microliter drop of blood placed on point of care testing strip for lactate testing by the hand-held device (Lactate Pro, FaCT, Canada). Lactate values are displayed on the device within 60 seconds. EMS providers will be blinded to the initial lactate as the display screen of the device will be obscured by a piece of tape. The machine reports values between 0.5-23.3 mmol/L.(1) Additional data will include the time of sampling, and the site of the sample. EMS providers will record the lactate value and any related information separate from the medical record after care has been transferred to the trauma team. EMS providers will be instructed to document the patient’s(2) initial vital signs and adherence to the inclusion/exclusion criteria of the study. No changes will be made to the EMS treatment protocols preventing any treatment changes based on the lactate value.

Hospital providers will be blinded to the point of care lactate values. A second point of care lactate will be obtained as soon as feasible upon ED arrival. The second lactate will be obtained using the same point of care device and will be taken from blood drawn during the initial trauma assessment. The site may operationalize this second point of care lactate by either asking EMS providers to run a second lactate from their point of care device or by requiring a hospital provider to run a point of care value in the trauma bay. These two values will be used to calculate a delta lactate, which, may be useful in predicting patient outcomes or evaluating the effectiveness of prehospital resuscitation. A delta lactate would not be recorded for patients that died in route to the hospital.

In addition, participating health systems have indicated that they routinely collect lab analyzed lactate levels in the trauma bay and we will protocolize that they do so on the first blood draw after patient arrival. The receiving care team will not be blinded to the result of a lactate measurement made as part of their routine trauma assessment.

If this study demonstrates the utility of lactate in the identification of patients suffering from the consequences of hypoperfusion, prehospital lactate will be incorporated into the screening procedures for future interventional trials. This study will be conducted by the Resuscitation Outcomes Consortium, (ROC), which is a collaboration of 10 regional sites in the United States and Canada and a Data Coordinating Center. This consortium is charged with the task of conducting prehospital clinical trials in patients with life threatening trauma and cardiac arrest. Selected ROC EMS agencies will participate in this study.

2. Specific Aims

2.1 Specific Aim

To compare prehospital lactate (P-LAC) levels to systolic blood pressure (SBP) $\leq 90$ in predicting the need for resuscitative care (the administration of packed red blood cells (PRBCs), emergent intervention for hemorrhage control with thoracotomy, laparotomy, pelvic fixation or interventional radiologic control) or death prior to or within 6 hours of ED arrival in patients with $70 < SBP \leq 100$ in the prehospital setting who have not received lactate ringers prior to lactate measurement.
2.2 Secondary Aim

To evaluate the usefulness of P-LAC, when combined with other prehospital variables (age, heart rate, systolic blood pressure, GCS, mechanism of injury), in predicting the need for resuscitative care.

Other aims are to determine whether prehospital lactate (P-LAC) levels predict mortality, emergent intervention for hemorrhage control, or massive transfusion (≥10 units of PRBCs) within 6 hours of ED arrival for patients with SBP between 70 and 100 and for patients with SBP ≤70.

3. Scientific Background

Previous studies have demonstrated the association between out-of-hospital hypotension, serious injury, and need for therapeutic interventions.(2-6) However, recent prospective out-of-hospital research has suggested the value of heart rate (HR) and field hypotension (i.e., systolic blood pressure, SBP ≤ 90 mmHg) in predicting the need for therapeutic interventions is less than previously thought.(7, 8) This is partly explained by the fact that in many patients, hypotension is a late finding and only manifests after a prolonged period of physiologic compensation. Furthermore, patients with head injuries, at the extremes of age, or being treated with certain medications (i.e. beta blockade) may not exhibit hypotension or tachycardia in response to traumatic injuries. This is concerning as these measures are currently used for triage of patients and enrollment in interventional trials of hemorrhagic shock. Applying traditional predictors of injury severity (e.g. Injury Severity Scoring (ISS) is not practical in the acute setting. Delayed identification of hypo-perfusion may lead to under-triage of some patients resulting in transport to inappropriate facilities or to inadequate or delayed resuscitation, which is strongly associated with increase in infection, multiple organ dysfunction (MOD), and mortality.(1, 5, 9)

There is also debate as to the appropriate criterion to define hypotension and tachycardia in the patient with hemorrhagic shock. Some investigators have advocated the use of a SBP of 110 mm Hg as the true definition of hypotension as mortality increases below blood pressures of this value.(10) Mechanistic criteria used to initiate therapy are neither sensitive nor specific and contribute to over triage while adding little benefit. Additional information from the scene of injury may facilitate more rapid and specific identification of seriously injured patients requiring definitive care.

Serum lactate is a byproduct of anaerobic metabolism as well as a circulating biomarker of organ oxygen supply/demand mismatch. Elevated lactate is associated with mortality in patients with sepsis, myocardial infarction, and trauma.(11-13) Trends in serum lactate levels can also monitor the effectiveness of resuscitation, even in patients with normal vital signs.(12, 13) Historically, measurement of serum lactate levels was costly, time-intensive, and restricted to a laboratory. Currently, technological advances have led to the production of handheld, point of care (POC) lactate analyzers that produce fast, reliable and valid measurements.(14) Use of POC lactate is now feasible in the out-of-hospital setting. Hospital- and emergency department-based studies have validated hand-held lactate devices,(15) demonstrated the value of lactate in intoxicated patients,(12) and suggested the potential utility of point-of-care lactate testing among trauma patients.(16-18) Despite these advances, out-of-hospital studies of point-of-care lactate testing in trauma patients is limited and the utility of field lactate in clinical management remains unclear.
4. Preliminary Studies

Previous studies have demonstrated that point of care lactate can predict post injury hemorrhage and that prehospital lactate is associated with need for hospital admission, ICU admission, emergent intervention and death.(1, 9) Vondromme et al. note that standard hemodynamic monitoring underestimates the severity of hemorrhage. They retrospectively reviewed 2,519 patient records from the trauma bay to identify those patients in need of massive transfusion (>6 units of PRBCs). Among patients with SBP <110, an increased need for massive transfusion was associated with increased lactate. Using adjusted risk ratios, the investigators demonstrated that lactate was superior to SBP alone for the identification of shock and suggested a prehospital trial of lactate measurement to confirm these results.(1)

Table: 1: Frequencies and adjusted RRs* (95% Confidence Interval) of blood lactate (BL) and need for 6 units PRBC within 48 hours post-injury stratified by SBP10

<table>
<thead>
<tr>
<th>SBP:</th>
<th>≤90</th>
<th>&gt;90–100</th>
<th>&gt;100–110</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td>174/600 (29.0)</td>
<td>67/539 (12.4)</td>
<td>68/983 (6.9)</td>
</tr>
<tr>
<td>Blood Lactate:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.5 (referent)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt;2.5–5.0</td>
<td>2.2 (1.2–3.6)</td>
<td>2.8 (1.5–4.9)</td>
<td>2.2 (1.3–3.8)</td>
</tr>
<tr>
<td>&gt;5.0–7.5</td>
<td>2.6 (1.5–4.4)</td>
<td>2.3 (1.0–5.1)</td>
<td>3.5 (1.8–6.8)</td>
</tr>
<tr>
<td>&gt;7.5</td>
<td>3.3 (2.0–5.6)</td>
<td>4.2 (2.0–8.9)</td>
<td>5.1 (2.5–10.5)</td>
</tr>
<tr>
<td>Trend p-value</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, ISS, and injury type

Among trauma patients, elevated prehospital lactate has been associated with increased mortality and hospital admission. The investigators hypothesized that prehospital lactate would predict severity of illness measured by death and ED disposition.(19) They prospectively observed 2,062 patients transported to a level I trauma center comparing lactate and traditional vital signs for their ability to predict patient mortality and hospital admission. Odds ratios for predictors of death were lactate (OR for an increase by one mmol/L 2.14; CI 1.19–3.85), HR (OR for an increase by 1 beat/minute 1.04; CI 1.02–1.05), and age (OR for each additional year 1.04; CI 1.02–1.07). Independent predictors of hospital admission were POC lactate (OR 1.43 for an increase by one mmol/L; CI 1.17–1.75), and age (OR 1.03 for each additional year; CI 1.02–1.04).(20) The authors concluded that lactate out performs all prehospital vital signs for the prediction of mortality and need for hospital admission. In a separate analysis of the same data set the authors conclude that standard hemodynamic variables do not correlate with prehospital lactate and that vital signs frequently underestimate elevated lactate levels.(19)

Point of care lactate has also been used in a large air medical system to identify consequences of hypoperfusion.(9, 21) In this retrospective, observational dataset, 400 trauma patients underwent both continuous vital sign monitoring and both prehospital and emergency department lactate sampling. Those patients with prehospital lactate levels >4 had greater need for emergent operation, intubation, and vasopressors. This association persisted even after adjustment for age, GCS, and initial vital signs.(21) A subsequent analysis of the data included only those patients with normal vital signs (SBP>100 and HR<100). Among the 265 patients without hypotension or tachycardia, those with lactates >4 had higher odds of an emergent operative procedure (OR 5, CI 1.5–16.2), MODS>6 (OR 2.34, CI 0.8–6.6), vasopressor requirement (OR 2.1, 0.6–6.9) and death (OR 3.5, CI 1.3–9.7) as compared to those with a lactate ≤4. ISS scores also differed significantly, patients with lactate levels >4 had mean ISS scores of 14.1 (CI 11.5, 16.6) while those with lactates <4 had mean ISS scores of...
10.6 (CI 9.3, 11.8) (P=0.008). Prehospital lactate strongly predicts death and the need for emergent surgery among trauma patients with normal vital signs. (9, 21)

The preliminary studies have demonstrated that point of care lactate predicts the severity of hemorrhage in the trauma bay, prehospital lactate is associated with increased mortality and the need for ICU admission, and patients transported in an air medical system with elevated lactate have higher odds of death independent of vital signs. Despite these data, we have not yet demonstrated that prehospital lactate is of additive benefit in the triage of trauma patients. This study will evaluate the ability of prehospital lactate to triage patients in need of resuscitative care that could not be otherwise identified by abnormal vital signs. In addition, a combination of lactate and vitals sign criteria may give advanced warning in a population of patients suffering from hemorrhage. Lactate may also identify patients with more severe illness who could potentially benefit from life saving interventions and novel therapies.

5. Study Methods

5.1 Primary Null Hypotheses

The null hypotheses are that lactate has the same (under the alternative hypothesis higher) sensitivity (without any concomitant loss of specificity) as SBP ≤ 90 to predict the need for resuscitative care (the administration of PRBCs, emergent intervention for hemorrhage control) or death prior to or within 6 hours of ED arrival in patients with SBP between 70 and 100 (70<SBP≤100) treated by ground or air medical services who have not received lactate ringers prior to lactate measurement.

5.2 Secondary Null Hypotheses

The secondary null hypotheses are that there is no association between P-LAC and the need for resuscitative care after taking other pre-hospital covariates into account.

5.3. Research Design

We propose a prospective observational study designed to identify patients suffering from the consequences of hypoperfusion. Blood testing is done only on those patients who have an IV placed. We anticipate the protocol to qualify for waiver from informed consent due to minimal risk. Data collection is based primarily on the Prospective Observational Prehospital and Hospital Registry for Trauma (PROPHET) study, this study (with POC lactate measurements) could potentially be submitted to IRBs/REBs as an addendum to the existing PROPHET protocol.

5.4 Setting

Patients will be recruited by EMS agencies with a limited number of ALS units responding to a high volume of patients with traumatic injury and SBP ≤100. Agencies that transport to a small number of trauma centers to facilitate data collection are ideal.

5.5 Inclusion Criteria

Patients meeting local trauma triage criteria, a systolic blood pressure ≤ 100, placement of an IV, and are transported to a level I or II trauma center, or died in the field or en route (with SBP≤100 and after placement of an IV).
5.6 Exclusion Criteria

Known prisoners, age < 15 years, obvious isolated penetrating head injury, hanging, drowning, primary burn related injury and blunt or penetrating injury with burns >20% of total body surface area.

5.7. Lactate Collection

After intravenous line (IV) placement but prior to the initiation of IV fluids in that IV line, each enrolled patient will have an approximately 5 microliter drop of blood placed on point of care testing strip for lactate testing by the hand-held device (Lactate Pro, FaCT, Canada). If a patient has already received fluid through an IV and an additional IV is indicated, the lactate should be sampled from the second IV upon insertion. The time of the lactate and the amount and type of fluid administered through the first IV at the point of sampling must be recorded. If no additional IV is indicated, the patient is excluded. Lactate values are displayed on the device within 60 seconds. EMS providers will be blinded to the initial lactate as the display screen of the device will be obscured by a piece of tape (see Appendix 1 and 2). The tape will be placed so that the value is not visible but the operator can identify if the machine has reported an error. If time permits the crew will be asked to rerun the sample if an error message is detected. The machine reports values between 0.5-23.3 mmol/L. Additional data will include the time of sampling and site of the sample. Following transfer of care to the trauma team, the EMS crew will record the lactate value and any related information separate from the medical record. No changes will be made to the EMS treatment protocols preventing any treatment changes based on the lactate value. A second point of care lactate will be obtained as soon as feasible upon ED arrival. The second lactate will be obtained using the same point of care device and will be taken from blood drawn during the initial trauma assessment. The site may operationalize this second point of care lactate by either asking EMS providers to run a second lactate from their point of care device or by requiring a hospital provider to run a point of care value in the trauma bay. These two values will be used to calculate a delta lactate, which, may be useful in predicting patient outcomes or evaluating the effectiveness of prehospital resuscitation. A delta lactate would not be recorded for patients that died in route to the hospital.

In addition, participating health systems have indicated that they routinely collect lab analyzed lactate levels in the trauma bay and we will protocolize that they do so on the first blood draw after patient arrival. The receiving care team will not be blinded to the result of a lactate measurement made as part of their routine trauma assessment.

5.8 Data Collection

A centralized web based data collection system will be used and maintained by the Data Coordinating Center. This will include baseline data, care process data and outcome data. A manual of operations will be created that will contain the data collection forms and detailed instructions. This investigation will be submitted as an ancillary study to PROPHET and subjects with a systolic blood pressure between 90-100 will also have PROPHET data collection forms completed.

In addition to the current PROPHET data points, data collection includes SBP prior to lactate blood draw, time and result of blood draws, fluid type and amount prior to lactate draw, total fluids and date and time of procedures (laparotomy, thoracotomy, pelvic fixation, or angiographic hemorrhage control) in the first 6 hours after ED arrival. We will also collect data for potential adverse events including transport delays and device problems and report protocol violations such as lactate draws without documented SBPs or lactates drawn on patients with
SBPs >100 unless otherwise directed by local protocol. In particular, we will collect data on age, mechanism of injury and prehospital heart rate, systolic blood pressure, and GCS as potential covariate for multivariable regression.

6. Study Outcome Measures

6.1 Primary Outcome Measure

Requirement for resuscitative care defined as the need for administration of PRBCs, emergent intervention for hemorrhage control (thoracotomy, laparotomy, pelvic fixation or interventional radiologic control) or death prior to or within 6 hours of ED arrival in patients with 70 < SBP ≤ 100 in the prehospital setting treated by ground or air medical services.

6.2 Secondary Outcome Measures

a) Mortality among patients with 70<SBP≤100 within six hours of ED arrival.

b) Mortality among patients with SBP≤70 within six hours of ED arrival.

c) Need for massive transfusion (greater than 6 units of PRBC’s), or death within six hours of ED arrival.

6.3 Exclusion Criteria

Known prisoners, age < 15 years, obvious isolated penetrating head injury, hanging, drowning, previous IV fluid administration, primary burn related injury and blunt or penetrating injury with burns >20% of total body surface area.

6.4 Lactate Collection

After intravenous line placement but prior to the initiation of IV fluids, each enrolled patient will have an approximately 5 microliter drop of blood placed on point of care testing strip for lactate testing by the hand-held device (Lactate Pro, FaCT, Canada). Lactate values are displayed on the device within 60 seconds. EMS providers will be blinded to the initial lactate as the display screen of the device will be obscured by a piece of tape (see Appendix 1 and 2). The tape will be placed so that the value is not visible but the operator can identify if the machine has reported an error. If time permits the crew will be asked to rerun the sample if an error message is detected. The machine reports values between 0.5-23.3 mmol/L. Additional data will include the time of sampling and site of the sample. Following transfer of care to the trauma team, the EMS crew will record the lactate value and any related information separate from the medical record. No changes will be made to the EMS treatment protocols preventing any treatment changes based on the lactate value. A second point of care lactate will be obtained as soon as feasible upon ED arrival. The second lactate will be obtained using the same point of care device and will be taken from blood drawn during the initial trauma assessment. The site may operationalize this second point of care lactate by either asking EMS providers to run a second lactate from their point of care device or by requiring a hospital provider to run a point of care value in the trauma bay. These two values will be used to calculate a delta lactate, which, may be useful in predicting patient outcomes or evaluating the effectiveness of prehospital resuscitation. A delta lactate would not be recorded for patients that died in route to the hospital.

In addition, participating health systems have indicated that they routinely collect lab analyzed lactate levels in the trauma bay and we will protocolize that they do so on the first blood draw after patient arrival. The receiving care team will not be blinded to the result of a lactate measurement made as part of their routine trauma assessment.
6.5 Data Collection

A centralized web based data collection system will be used and maintained by the Data Coordinating Center. This will include baseline data, care process data and outcome data. A manual of operations will be created that will contain the data collection forms and detailed instructions. This investigation will be submitted as an ancillary study to PROPHET and subjects with a systolic blood pressure between 90-100 will also have PROPHET data collection forms completed.

In addition to the current PROPHET data points, data collection includes SBP prior to lactate blood draw, time and result of blood draws, fluid type and amount prior to lactate draw, total fluids and date and time of procedures (laparotomy, thoracotomy, pelvic fixation, or angiographic hemorrhage control) in the first 6 hours after ED arrival. We will also collect data for potential adverse events including transport delays and device problems and report protocol violations such as lactate draws without documented SBPs or lactates drawn on patients with SBPs >100 unless otherwise directed by local protocol. In particular, we will collect data on age, mechanism of injury and prehospital heart rate, systolic blood pressure, and GCS as potential covariate for multivariable regression.

7. Sample Size
7.1 Primary Outcomes

For patients with SBP between 70 and 100 (70<SBP≤100) data from the air medical services in Pittsburgh (Table 2) show the following relationship between a systolic blood pressure cutpoint of ≤ 90 and a lactate cutpoint of ≥ 3.3 for patients who needed resuscitative care (the administration of packed red blood cells (PRBCs), emergent intervention for hemorrhage control using thoracotomy, laparotomy, pelvic fixation or interventional radiologic control) or died prior to discharge.

Table 2: Pittsburgh Relationship between SBP & Lactate Level

<table>
<thead>
<tr>
<th>SBP</th>
<th>Lactate</th>
<th>&gt; 90</th>
<th>≤ 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.3</td>
<td>14 (25.9%)</td>
<td>7 (13.0%)</td>
<td>21 (38.9%)</td>
</tr>
<tr>
<td>≥ 3.3</td>
<td>14 (25.9%)</td>
<td>19 (35.2%)</td>
<td>33 (61.1%)</td>
</tr>
<tr>
<td></td>
<td>28 (51.9%)</td>
<td>26 (48.2%)</td>
<td>54 (100.0%)</td>
</tr>
</tbody>
</table>

The sensitivity of a lactate of 3.3 is 61.1% (33 out of 54). The sensitivity of SBP ≤ 90 is 48.2% (26 out of 54). The specificity for both is 65.4%. As a result, the difference in sensitivity in this setting is 12.9% (61.1%-48.2%), while the proportion of discordant pairs is 38.9% (13.0%+25.9%). Such a difference in sensitivity (with the same proportion of discordant pairs) would yield 90% power based on 235 patients with SBP between 70 and 100 for a two-sided McNemar’s test with alpha=0.025. These estimates provide the basis for the comparison of prehospital lactate and SBP in patients treated by air medical services. Estimates were obtained using the software East, version 5.2.
Under similar assumptions (two-sided test with alpha=0.025) the study has about 90% power to detect a difference in sensitivity of 10.5% if 360 patients with SBP between 70 and 100 are enrolled via ground medical services.

We anticipate that it will be possible to enroll sufficient number of patients treated by air medical or ground services within about one year. We will continue to recruit patients treated by ground and air medical services until both sample sizes (235 for air with 70<SBP≤100, and 360 for ground with 70<SBP≤100) are met. If one of the groups (air or ground) achieves the required sample size much earlier than the other group, we will consider terminating enrollment in this group while continuing to enroll in the other. We anticipate enrolling 595 patients with 70<SBP≤100 and enrolling a total of about 970 patients with SBP≤100 (i.e. about 375 patients with SBP≤70).

We are testing the utility of lactate separately for ground and air medical services because of the difference in time from 911 call to arrival of the emergency medical services, differences in characteristics of patients enrolled (e.g. patients who die soon after arrival of the first responding unit are unlikely to be treated and transported by air medical services) and differences in training and potential for advanced care during transport.

8. Analysis Plan

8.1 Primary Hypotheses

We will use the McNemar’s test to compare sensitivity of SBP ≤ 90 at a lactate cut point, which has the same specificity as SBP ≤ 90. This analysis will be performed separately for patients treated by ground and air medical services (two-sided tests with α=0.025 for each test) and exclude patients who received lactated ringers prior to lactate measurement.

8.2 Secondary Hypotheses

Analyses to compare the performance of prehospital lactate measure and SBP for additional outcomes will also be done. Descriptive statistics for lactate level; baseline and prehospital characteristics will be reported. Univariate comparisons will be made between outcome groups using t tests, and chi-squared tests.

In addition, we will also explore a range of cut points based on the intended use of the lactate measure. Triage of patients to a trauma center may warrant a lower lactate cut point to maximize sensitivity while inclusion criteria for an interventional trial may necessitate a higher cut point in order minimize exposure to a potentially risky treatment.

Patients who have lactate measures obtained by both ground and air medical services will be considered as part of the ground comparison. A secondary analysis will be performed to compare sensitivity of SBP ≤ 90 at a lactate cutpoint which has the same specificity as SBP ≤ 90, but is restricted to patients who did not receive any fluid prior to lactate measurement.

To assess for independent association of lactate level with primary outcomes, a multivariable logistic regression model will be examined adjusting for initial and worst prehospital heart rate, blood pressure, shock index, and pulse pressure. These variables were chosen because they are the most common prehospital signs used for triage of trauma patients. Other covariates to consider include time of transport, time from dispatch to acquisition, age, GCS and mechanism of injury (blunt versus penetrating).
In exploratory analyses classification and regression tree (CART) approaches will be used to investigate whether a combination of factors might improve the identification of patients with a need for advanced care. Technically, depending on effect size and number of patients enrolled a large number of factors might be identified as important predictors through either CART or logistic regression models. Nevertheless, any approach or rule to identify patients for triage or enrollment into clinical trials will need to satisfy the following two crucial criteria: 1) all factors can quickly and reliably be obtained in the pre-hospital setting and 2) the rule/approach needs to be simple enough to be implementable in a quick and easy way.

8.3 A priori Subgroup Analysis

The following a priori subgroup analyses will be considered: Stratified analyses of field hypotension (SBP <70, 70-89, 90-100mmHg).

a) Age (15-55, > 55 years).

b) Injury type (blunt vs. penetrating).

c) Time from dispatch to lactate value (≤ 30 min, > 30 min).

d) Amount of fluid received (<0.5L, 0.5-1L, >1L) prior to second lactate level.

e) Type of fluid-LR vs. NS.

8.4 Plan for Missing Data

The primary analysis will be based on all complete cases. Sensitivity analyses for missing covariates will be performed using multiple imputation methods. Because the time frame for outcome measures is short (within 6 hours of ED arrival) the amount of missing values is anticipated to be small.

8.5 Monitoring of Adverse Events

A quality assurance program will be implemented to identify any inappropriate enrollments, or violations of the protocol. Participating crews will also be required to report any difficulty in obtaining samples or multiple IV attempts. We will also monitor on-scene times for participating agencies and compare these to on-scene times prior to the start of the Lactate study to investigate whether collection of the lactate sample leads to delays in patient transport. All adverse events will be reported to the DSMB and IRBs according to usual practice. Adverse events may include delay of care or complications of IV line placement. Because of the observational nature of the study and the anticipated length (about one year), there will be no formal interim analysis. Nevertheless, descriptive statistics regarding enrollment and key aspects of the study will be reported to the ROC DSMB during their regularly scheduled meetings as determined by the DSMB.

8.6 EMS Training

All agencies will be required to document device calibration once each week as recommended by the company as well as evaluating the device with a quality assurance test strip when using a new box of 25 strips.

The method for blood sample collection and analysis will require minimal additional training as it is identical to the technique used to obtain and analyze blood glucose samples. Agencies participating in the study will undergo an in-service on the device including a review of blood sampling techniques, use of the point of care lactate meter, and procedures for quality control
and care of the meter. Participants will be asked to record the patient’s vital signs and document adherence to the inclusion and exclusion criteria of the study.

Participating services will be required to adhere to their local protocols. Following transfer of care of the patient the prehospital and ED P-LAC values will be recovered from the meter and recorded on their study documentation forms. The receiving clinicians will be blinded to the prehospital and second P-LAC values as it will not be reported to them by EMS.

8.7 Potential Impact on ROC

As this is an observational study, it does not require a large investment in resources or material (training, lactate meters and strips). Data collection will be identical to PROPHET for the majority of data items. As no intervention is planned, this study will not interfere with any other ROC study. If P-LAC is shown to predict those patients who require extensive intervention or poor outcome it may provide alternative inclusion criteria for future trauma studies.

8.8 Anticipated Significance

In trauma patients, measurement of serum lactate levels at the scene of the injury and prior to ED arrival may provide improved prognostic information about in-hospital morbidity, mortality and resource utilization. This study can prospectively validate previous experience in unselected trauma patients. Future implementation might include using prehospital lactate as part of a decision aid to identify and direct the need for aggressive prehospital and emergency department resuscitation. Prehospital lactate measurement may also provide a more efficient mechanism for identifying potential subjects for studies of trauma interventions.

8.9 Participating ROC Sites and Agencies

Criteria for EMS Agency Participation:

a) Ability to obtain waiver of consent for minimal risk from IRB.
b) Small number of level 1 or 2 hospitals to collect data from.
c) Hospital must collect lactate routinely or be willing to change for participation in the study.
d) EMS or hospital personnel are willing to draw a second lactate (with the P-LAC device) at the same time the first blood lactate is drawn in the ED.
e) Lower ratio of vehicles to trauma transportations thus requiring a smaller number of devices.
f) Inexpensive and rapid training of EMS.
g) Ability to collect time of IV insertion/time of prehospital lactate collection.
h) Review of HS participation shows adequate time to notification of cases, timeliness of data entry, few protocol violations, limited missing inventory, etc.

9 Human Subjects Research

9.1. Waiver of Informed Consent for Participation

A relevant Institutional Review Board in the United States (or Canadian equivalent) can approve a waiver of the usual requirements of informed consent, provided that it finds and documents that:
The research involves no more than minimal risk to the subjects. The proposed ROC study involves no intervention. All victims suffering traumatic injury will receive standard treatment by EMS personnel in the field and ED personnel. There is no risk to the subjects, except possibly a breach of confidentiality or a brief delay in transport. We have taken extensive steps to manage and minimize this risk according to a range of recognized best practices and in conformity with prevailing regulations, policies and laws in the United States and Canada. A drop of blood (less than 5 microliters) is required for the treating paramedic to obtain a lactate. Lactate would only be collected on trauma patients who require an IV for their standard trauma care. No additional IV catheter placement will be required to measure lactate values. The blood sample would be obtained from the IV needle hub and would not pose any additional risk to the patient. Pre-hospital care providers and clinicians at the receiving hospital will be blinded to the prehospital lactate value. The process of obtaining the lactate takes approximately 60 seconds and should not delay patient transport. We will monitor transport times to ensure there are no clinically significant delays. The collection of data for this study is limited to information in patient charts obtained during routine, standard care. IRB-approved standards and practices for study data collection, storage, and retrieval are in place through the Resuscitation Outcomes Consortium Data Center, University of Washington to minimize the loss of confidentiality and privacy with the data collected during this study.

The waiver will not adversely affect the rights and welfare of the subjects. The study has not and will not affect patient care, as this is an observational study and these patients have already had their recommended care when the lactate values are recorded and the data collected.

The research could not be practicably carried out without waiver of consent. Persons being enrolled in the lactate study cannot consent to participate because they have an acute life-threatening illness that requires immediate treatment. To avoid selection bias in creating a robust dataset that describes patients with out-of-hospital life-threatening illness, the characteristics of all trauma patients that meet the inclusion criteria must be determined. The act of obtaining consent will introduce significant bias in that survivors are available to provide consent, but those who die early following injury are unavailable. These high-risk patients are critical to provide an understanding of risk factors for death or disability after out-of-hospital life-threatening illness. Subjects and/or their legal next of kin might not be identified for days following injury almost assuring that this bias will occur should consent be a requirement for data collection.

Whenever appropriate, the subjects will be provided with additional pertinent information after participation. As there are no direct identifiers used in the performance and reporting of this research, it will not be possible to provide those subjects whose data are being used with any information about the research. Information gathered from this study will be shared with the community at large upon publication.

The waived or altered consent does not involve a therapeutic intervention. (Tri-Council Policy Statement. Ethical Conduct for Research Involving Humans, Ottawa: Medical Research Council, Social Sciences and Humanities Research Council, Natural Sciences and Engineering Research Council, 1998, Section 2.1(c).) In the data collection for the proposed lactate measurement, the research subjects will not receive any experimental intervention, but will receive standard care in the field.
9.2 Plan for Missing Data

The primary analysis will be based on all complete cases. Sensitivity analyses for missing covariates will be performed using multiple imputation methods. Because the time frame for outcome measures is short (within 6 hours of ED arrival) the amount of missing values is anticipated to be small.

9.3 Monitoring of Adverse Events

A quality assurance program will be implemented to identify any inappropriate enrollments, or violations of the protocol. Participating crews will also be required to report any difficulty in obtaining samples or multiple IV attempts. We will also monitor on-scene times for participating agencies and compare these to on-scene times prior to the start of the Lactate study to investigate whether collection of the lactate sample leads to delays in patient transport. All adverse events will be reported to the DSMB and IRBs according to usual practice. Adverse events may include delay of care or complications of IV line placement. Because of the observational nature of the study and the anticipated length (about one year), there will be no formal interim analysis. Nevertheless, descriptive statistics regarding enrollment and key aspects of the study will be reported to the ROC DSMB during their regularly scheduled meetings as determined by the DSMB.

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e) Inexpensive and rapid training of EMS.

f) Ability to collect time of IV insertion/time of prehospital lactate collection.

g) Review of HS participation shows adequate time to notification of cases, timeliness of data entry, few protocol violations, limited missing inventory, etc.
References


Appendix 1: Blinded Lactate Value

Appendix 2: Lactate Error Message