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Publication Date

2024-04-15

Supplemental Material

https://escholarship.org/uc/item/9759s05h#supplemental

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Potential medical impact of unrecognized *in vitro* hypokalemia due to hemolysis: a case series

Abstract

Objectives: The destruction of red cells during blood collection or with the processing of the sample continues to occur at a high rate, especially among emergency department (ED) patients. This can produce pre-analytical laboratory errors, particularly for potassium. We determined the incidence of hemolyzed samples and discuss the potential medical impact for hypokalemic patients who potassium level is artificially normal (pseudoeukalemia).

Methods: Potassium results were obtained for a 6-month period. Using a measured hemolysis index (HI), hemolysis was present in 3.1 % for all potassium ordered (n=94,783) and 7.5 % for ED orders (n=22,770). Most of these samples were reported as having high normal result or were hyperkalemic. There were 22 hemolytic samples with a potassium of <3.5 mmol/L, and 57 hemolytic samples with a potassium in lower limit of normal (3.5–3.8 mmol/L). From this group, we examined the medical histories of 8 selected patients whose initially normal potassium levels were subsequently confirmed to have a potassium values that were below, at, or just above the lower limit of normal due to hemolysis.

Results: The primary complaint for these patients were: necrotizing soft tissue infection, pancreatitis, volume overload from heart failure with reduced ejection fraction, hypertension treated with hydrochlorothiazide, and presence of a short bowel syndrome. A subsequent non-hemolyzed sample was collected demonstrating hypokalemia in all of these patients. Within these cases, there was a potential for harm had hemolysis detection not been performed.

Conclusions: We demonstrate the medical importance of detecting hemolysis for patients who have pseudoeukalemia. This is relevant because the HI cannot be obtained when electrolytes are tested using whole blood samples, and a normal potassium may lead to inappropriate patient management.

Introduction

Hemolysis is defined as a destruction of red blood cells (RBCs) releasing hemoglobin and other cellular constituents such as potassium into the circulation [1]. *In vivo* hemolysis is the premature breakdown of RBCs within the circulation that are caused by underlying congenital and acquired medical conditions. *In vitro* hemolysis refers to pre-analytical issues that damage RBCs during blood collection or in the processing of the sample itself. Calleja et al. reported a hemolysis rate of 17.2 % from over 140,000 records reviewed [2]. Phelan et al. hemolyzed blood samples occured in 13 % of patients from over 11,000 medical records reviewed. The presence of this form of hemolysis often triggers a sample re-collection. Repeat collections is not without consequence. In one study of 11,000 medical records, Phelan showed that the length of stay (LOS) increased by 62 min for patients with hemolyzed samples vs. those without [3].

There are several laboratory tests that are affected by hemolysis. The red color of hemoglobin can interfere with assays that rely on the measurement of absorption in the visible region of the spectrum. Hemoglobin itself can cause a chemical interference due to its oxidant reactions. RBC constituents such as potassium, lactate dehydrogenase, aspartate aminotransferase and magnesium are released into blood following hemolysis and can produce additional false positive increases. The clinical laboratory thus has the responsibility of noting the presence of hemolysis for any serum or plasma samples tested. Automated detection can be accomplished by measuring the absorbance at the appropriate wavelength of hemoglobin (e.g., 405 nm).

Hemolysis causes an increase in potassium and can move a normal result into an abnormal result (pseudohyperkalemia). Within the report, most laboratories will flag the hemolysis and high potassium. In contrast, when the potassium is low, hemolysis can move the result to normal

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(pseudoeukalemia). Like hyperkalemia, true hypokalemia is not a rare finding among ED patients. In a report by Singer et al., of 100,260 ED patients, 2,574 (2.6 %) had a potassium of <3.5 mmol/L [4]. Potassium concentrations<3.5 mmol/L were associated with a 1.6-fold increased risk of in-hospital mortality proportional to the severity of the abnormality (the lower the potassium, the more likely the patient was to suffer mortality). If the attending staff does not see the warning that a sample is hemolyzed, they may not realize their patient has hypokalemia, as the normal potassium result itself is not flagged. Patients with either pseudohyperkalemia and pseudoeukalemia are associated with increased mortality compared to a normal potassium result.

The purpose of this report is to determine the hemolysis rate at a large general hospital and review cases of patients who presented with a normal potassium in the context of pseudoeukalemia. Of critical consequence is that hemolysis detection cannot be made when electrolyte testing is conducted using blood gas analyzers which make use of whole blood samples. This problem has been previously documented in high risk patient groups such as children [5], the ED and ICU [6] where the rate of hemolysis from whole blood testing were unacceptably high. The presence of true hypokalemia may have been missed resulting in no treatment for potentially life-threatening conditions. The medical significance of this situation is discussed.

Materials and methods

This study was conducted at the Zuckerberg San Francisco General Hospital. This is a large Level 1 trauma center that serves an indigent population with a high rate of infectious diseases and drug abuse. This protocol was reviewed and approved by the University of California Institutional Review Board, who deemed that individual patient consent was not required. Blood samples were collected into evacuated serum separator tubes (Becton Dickinson, Franklin Lakes, NJ, USA) and were sent to the clinical laboratory via pneumatic tubes. Sodium and potassium measurements were made using the Atellica Chemistry Analyzer (Siemens Healthineers, Erlangen, Germany) using standard ion selective electrode technologies.

Electrolyte data was obtained from the Clinsys Laboratory Information system (Tucson, AZ, USA) in place at Zuckerberg San Francisco General (ZSFG) Hospital. The reference range is 136–145 mmol/L for sodium and 3.5–5.1 mmol/L for serum potassium. Typically, serum potassium results are slightly higher than plasma due to the release of a small amount of potassium during the clotting process [7]. This is why the upper limit of potassium of 5.1 mmol/L used for many years at ZSFG is slightly higher than the more typical upper reference limit value of 5.0 mmol/L. The total number of potassium tests were obtained from July 1, 2023 to December 31, 2023. The electrolyte results were obtained as part of orders for a basic and comprehensive metabolic panel, renal panel, or as an individual serum potassium test. There was also electrolyte testing conducted on whole blood collected with syringes

anticoagulated with heparin (GEM 5000, Werfen, Bedford, MA, USA) but, as there is no means to determine hemolysis from whole blood samples, this data was not included in the overall rate of sample hemolysis. However, whole blood electrolyte testing from the case reports is included.

There are six levels of hemolysis noted by the Atellica analyzer. Those noted in zones +1, +2, and +3 contain hemoglobin concentrations of 11–130, 131–249, and 250–499 mg/dL, respectively [8]. Those in zones +4 and +5 have hemoglobin concentrations of 500–749 and 750–999 mg/dL, respectively. Zone +6 has hemoglobin concentrations of ≥1,000 mg/dL. The policy at ZSFG is that potassium results that fall within this last zone are not reported. Using two different models, Mansour et al. previously showed that the potassium concentration increases from 0.40 to 0.51 mmol/L per 100 mg/dL of free hemoglobin [9]. Using the median values for each HI index zone, and the lower 0.40 value for the expected hemoglobin increase due to hemolysis, the potassium concentrations are expected to increase by 0.3, 0.8, and 1.7 mmol/L for zones of +1, +2, and +3, respectively.

In each of our cases, the electrolyte measurements were made on serum at the initial presentation of the patient to the ED using a central laboratory analyzer. We reviewed the medical records for patients where a hemolytic sample was obtained and the patient had normal potassium results in the lower end of the reference range, defined as 3.5–3.8 mmol/L (i.e., a pseudoeukalemic patient). It was presumed that these patients had hypokalemia that was masked by the contribution of potassium from the hemolysis. The ED records of 8 of these selected cases were reviewed (Epic Electronic Medical Records System, Verona, WI, USA). Some of the electrolyte measurements were made using whole blood. Because the HI was not available, a determination of the hemolysis status for these samples was presumed based on the serial electrolyte test results. For comparison, we also determined the number of samples that had a potassium result from hemolyzed samples that was just above upper limit of the reference range, i.e., 5.2–5.5 mmol/L, defined as pseudohyperkalemia.

Results

There was a total of 94,783 orders for potassium testing during the 6-month observation period. Of these, 22,770 (24.0 %) were orders from the ED. There were 2,943 (3.1 %) and 1,713 (7.5 %) cases of hemolysis (+1 to +5) for the total and ED patients, respectively. There were 22 samples that had a potassium of <3.5 mmol/L, and 13, 16, 14, and 14 with potassium results at 3.5, 3.6, 3.7, and 3.8 mmol/L, respectively, for a total of 79 patients from the entire set. For the subset of potassium results from the ED, the corresponding number of cases were 9, 7, 7, 9, and 8 for the <3.5, 3.5, 3.6, 3.7 and 3.8 mmol/L, bin, respectively. In contrast, the number of patients who had an increased potassium (between 5.1 and 5.5 mmol/L) was 503 from the total and 269 for the ED subset. These latter groups of subjects were not the focus of this study, as pseudo-hyperkalemia is well recognized as a source of pre-analytical error in samples demonstrating hemolysis. Table 1 summarizes the medical cases of pseudoeukalemia, and Table 2 lists the initial and subsequent electrolyte

Table 1: Summary of case reports of pseudoeukalemia.

Case #1. 31-year-old female. Presents with right lower extremity cellulitis and possible necrotizing soft tissue infection.
Case #2. 21-year-old female. Presents with a history of pancreatitis and type I diabetes.
Case #3. 46-year-old male. Presents with hypertriglyceride-induced pancreatitis with a history of alcohol use disorder.
Case #4. 57-year-old female. Has a history of chronic obstructive pulmonary disease, liver cirrhosis, stimulant abuse disorder, HIV, fractures, and obesity, and currently presents with volume overload and heart failure with reduced ejection fraction. The patient is scheduled for treatment of HF with diuretics.
Case #5. 66-year-old male. Presents with shortness of breath and chest pain. Has a history of heart failure with preserved ejection fraction, stroke, bipolar disorder, substance abuse disorder, and hypertension.
Case #6. 61-year-old male. Presents with stage 4C heart failure with reduced ejection fraction, acute kidney injury and hypokalemia.
Case #7. 69-year-old female. Presents with dizziness. She has a history of hypertension treated with hydrochlorothiazide.
Case #8. 41-year-old female. Presents after a motor vehicle accident. Has a history of short bowel syndrome.

Table 2: Electrolyte results for reported cases.

	Sodium	Potassium	Hemolysis
Case #1			
Presentation	135	3.5	Yes
24 min	132 ↓	2.8 ↓	Presumed no[a]
7 h, 53 min	137	3.2 ↓	No
9 h, 44 min	140	3.7	No
Case #2			
Presentation	127 ↓	3.6	Yes
11 min	135	2.9 ↓	Presumed no[a]
46 min	131 ↓	3.8	No
Case #3			
Presentation	124[b] ↓	5.1	Yes
18 min	132 ↓	4.2	No
5 h, 52 min	135	4.8	Grossly hemolyzed
10 h, 46 min	132 ↓	4.9	Yes
13 h, 19 min	131 ↓	3.9	Yes
15 h, 34 min	133 ↓	3.0 ↓	No
Case #4			
Presentation	143	3.5	Yes
29 min	136	2.7 ↓	Presumed no[a]
23 h, 30 min	145	3.4 ↓	No
Case #5			
Presentation	132 ↓	3.3 ↓	Yes
50 min	128 ↓	2.4 ↓	Presumed no[a]
18 h, 50 min	136	3.4 ↓	No
Case #6			
Presentation	135	2.9 ↓	No
7 h, 49 min	134	2.9 ↓	No
14 h, 0 min	134	3.7	Yes
15 h, 44 min	136	3.5	No
Next day admission	129 ↓	3.3 ↓	No
2 min	129 ↓	2.8 ↓	Presumed no[a]
Case #7			
Presentation	135	2.8 ↓	Yes
7 h, 37 min	137	3.5	Yes
7 h, 40 min	136	2.5 ↓	Presumed no[a]
Case #8			
Presentation	127 ↓	3.5	Presumed yes[a]
43 min	137	3.6	Yes
8 h, 16 min	134	2.8 ↓	No
53 h, 11 min	137	3.2 ↓	No

[a]Whole blood analysis. [b]Sample is hyperlipidemic (causing pseudo-hyponatremia).

measurements and the actual via testing, and presumed hemolysis status. The time interval between the first and subsequent samples indicate the acknowledgment by the ED staff of the hypokalemic event, and the timing of potassium to repletion.

Case presentations

Case #1 had necrotizing soft tissue infections (NSTI). This condition can trigger a hypokalemia [10]. The decreased levels of sodium, potassium, calcium, hematocrit, pH, total protein, and albumin portend a poor progress. The initial normal potassium and sodium results in our case suggested that the patient was not at risk for NSTI complications. However, the note of hemolysis alerted the care team to check further. Twenty four minutes later, there was a recollection of blood and low values for sodium and potassium was obtained. Note that the drop in potassium (7 units) was disproportionate to the low sodium (3 units). Without the hemolysis check, further workup might not have occurred. At discharge, the patient was ruled out for NTSI and vomiting was determined to be the cause of her low potassium, attributed to possible anaphylactic reactions as a consequence of a CT scan radiocontrast and medications that was needed for the patient.

Hypokalemia and hypocalcemia are associated with severe pancreatitis and the presence of persistently low

electrolytes levels is associated with increased mortality. Signs of low potassium include muscle weakness, hypotension, and arrhythmia [11]. For case #2, the team recognized the potential interference with hemolysis and repeated testing for electrolytes at 11 min. The patient was hospitalized and given potassium supplements. The repeat potassium test from whole was in the normal range. Without the hemolysis check, she might have been inappropriately discharged.

For patient #3, the patient initially presented with a high normal and normal potassium. Then beginning around 6 h, several specimens were hemolyzed, including one that was grossly hemolyzed with a potassium of 4.8 mmol/L. A specimen with a +5 or +6 HI can contribute 2–3 mmol/L of potassium, suggesting that this sample was within the hypokalemia range. It was not until 15.5 h later that a non-hemolyzed sample was obtained and a confirmation of hypokalemia was made.

For case #4, the ED team recognized the hypokalemia within 29 min with a repeat potassium on a sample that was not hemolyzed. The patient was treated with potassium, resulting to near normalization. In the discharge summary, there was a note indicating that electrolyte repletion was needed prior to diuresis (which is well known to deplete potassium). There is a second note indicating that the team should avoid prescribing drugs that are known to be associated with a prolonged QT interval on electrocardiogram in the setting of hypokalemia. This is because potassium levels of <3.0 mmol/l cause significant QT interval prolongation which carries the subsequent risk of torsade des pointes, ventricular fibrillation and sudden cardiac death. Since anti-depressant drugs are known to affect the QT interval [12], which can be exacerbated in the presence of hypokalemia [13], these drugs should be avoided in clinical scenario like these. The patient had a history of treatment with bupropion and quetiapine. Without knowledge of the patient's hypokalemia, inappropriate timing and type of treatment could have resulted in an adverse and potentially fatal QT prolongation consequence.

Clinical laboratories maintain a list of critical values that prompt a call to the provider should a laboratory result drop below or above pre-established limits. For potassium, the lower critical value limit has been reported to be between 2.7 and 3.0 mmol/l [14]. At ZSFG, the lower limit is 3.0 mmol/L. Case #5 had an admission potassium of 3.3 mmol/l on a hemolyzed sample. While this value was low, the presence of the interferent increased the potassium to a level that was above the reportable critical range, and therefore a call was not made. It was 50 min before a repeat potassium was conducted which revealed a life-threatening potassium value of 2.4 mmol/L. Fortunately, this patient survived with no long-term complication.

Patient #6 presented with hypokalemia from two non-hemolyzed samples and was treated with potassium replacement. The cause was due to his heart failure treatment with

bumetadine and chlorthalidone, which had been recently added to his regimen. The morning after admission, the lab reported a normal potassium on a hemolyzed specimen. From this value, the team could not conclude that his potassium was normalized. A subsequent test about 100 min later on a nonhemolyzed specimen indicated his potassium value to be at the low end of normal. At that point, the patient left against medical advice, but returned the next day with symptoms of hypokalemia. There were two low potassium reading on non-hemolyzed specimens.

Patient #7, with a history of hydrochlorothiazide diuretic use for hypertension, presented with a critical potassium value of 2.8 mmol/L. Thiazide diuretics are known to produce hypokalemia. Using the 1999–2018 NHANES database, Lin et al., reported that hypokalemia was found in 12.6 % of the hydrochlorothiazide users (~2 million US adults). Women (aOR, 2.22; 95 % CI, 1.74–2.83), non-Hispanic blacks (aOR, 1.65; 95 % CI, 1.31–2.08), those who were underweight (aOR, 4.33; 95 % CI, 1.34–13.95), and patients using hydrochlorothiazide for at least 5 years (aOR, 1.47; 95 % CI, 1.06–2.04) had a higher risk of hypokalemia [15]. Our patient had each of these risk factors. However, as the initial sample was hemolyzed, the degree of hypokalemia was greater than reflected by the initially erroneous potassium result. While the patient was appropriately treated with replacement, resulting in a potassium level at the lower limit of normal 7 h later, the second sample was also hemolyzed, suggesting that the treatment was incomplete. A new specimen was collected a few minutes later that was not likely hemolyzed (whole blood specimen tested), and produced a potassium result of 2.5 mmol/L. The patient was then given more potassium and discharged without further testing. If the hemolysis status had not been known, the patient may have been inappropriately discharged with potentially life-threatening hypokalemia.

Electrolyte disturbances are also common in patients with short bowel syndrome due to a decrease in the absorption of vitamins and electrolytes [16]. While hypomagnesemia is a common and recognized effect, about 50 % of these patients also have hypokalemia. For patient #8, the first two hemolyzed samples produced a normal potassium result. It would be several hours before a repeat collection produced a nonhemolytic sample and the documentation of hypokalemia established.

Discussion

Most contemporary blood gas analyzers are used in critical care areas and emergency departments (EDs) to produce results within minutes of collection with point of care testing (POC) platforms. For blood gas analysis, this is particularly important because these parameters are unstable. Also, the gases and pH can change rapidly, requiring immediate management decisions. Today, these analyzers can also measure

electrolytes using the same whole blood sample to provide fast results as they obviate the need for delivery of the sample to the clinical laboratory, centrifugation, and testing on serum or plasma chemistry analyzers. However, a limitation of these POC analyzers is that they cannot detect the presence of hemolysis, since whole blood is highly pigmented therefore the presence of a small amount of free hemoglobin is obscured.

The best approach to minimize the misinterpretation of potassium testing in the presence of hemolysis is to eliminate this interferent altogether. Unfortunately, there are dozens of causes of hemolysis. These include patient-dependent factors including sample collection technique, specimen handling, transportation, processing, and storage [1]. While education can reduce the pre-analytical error rate, because there are many individuals involved in the process, such gains are usually short-lived. Testing of whole blood may be less subject to hemolysis, as some of the later steps are eliminated (e.g., pneumatic tube transfer, centrifugation, etc.) with point-of-care analysis. However, patient factors and blood collection procedures remain as sources of pre-analytical error. Ideally, if a future technology could be developed to report hemolysis for whole blood assays, the challenge of pseudoeukalemiacould be detected and leading to appropriate medical decisions.

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