Study design of real world evidence for treatment of hyperkalemia in the emergency department (REVEAL-ED): A multicenter, prospective, observational study

Zubaid Rafique  
*Baylor College of Medicine*

Mikhail Kosiborod  
*University of Missouri-Kansas City*

Carol Clark  
*Beaumont Hospital*

Adam Singer  
*Stony Brook School of Medicine*

Stewart Turner  
*ZS Pharma, Inc.*

*See next page for additional authors*

Follow this and additional works at: [https://digitalcommons.wustl.edu/open_access_pubs](https://digitalcommons.wustl.edu/open_access_pubs)

Please let us know how this document benefits you.

**Recommended Citation**

Rafique, Zubaid; Kosiborod, Mikhail; Clark, Carol; Singer, Adam; Turner, Stewart; Miller, Joseph; Char, Douglas; and Peacock, W. Frank, "Study design of real world evidence for treatment of hyperkalemia in the emergency department (REVEAL-ED): A multicenter, prospective, observational study." *Clinical and Experimental Emergency Medicine*. 4, 3. 154 - 159. (2017).  
[https://digitalcommons.wustl.edu/open_access_pubs/10982](https://digitalcommons.wustl.edu/open_access_pubs/10982)
Authors
Zubaid Rafique, Mikhail Kosiborod, Carol Clark, Adam Singer, Stewart Turner, Joseph Miller, Douglas Char, and W. Frank Peacock
Study design of Real World Evidence for Treatment of Hyperkalemia in the Emergency Department (REVEAL-ED): a multicenter, prospective, observational study

Zubaid Rafique¹, Mikhail Kosiborod², Carol L. Clark³, Adam J. Singer⁴, Stewart Turner⁵, Joseph Miller⁶, Douglas Char⁷, W. Frank Peacock¹
on behalf of the REVEAL-ED study investigators

¹Ben Taub General Hospital, Baylor College of Medicine, Houston, TX, USA
²Saint Luke’s Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, MO, USA
³Beaumont Hospital-Royal Oak, Royal Oak, MI, USA
⁴Stony Brook School of Medicine, Stony Brook, NY, USA
⁵ZS Pharma, Inc., San Mateo, CA, USA
⁶Henry Ford Hospital, Detroit, MI, USA
⁷Washington University, Saint Louis, MO, USA

Objective Hyperkalemia affects up to 10% of hospitalized patients and, if left untreated, can lead to serious cardiac arrhythmias or death. Although hyperkalemia is frequently encountered in the emergency department (ED), and is potentially life-threatening, standard of care for the treatment is poorly defined, with little supporting evidence. The main objectives of this observational study are to define the overall burden of hyperkalemia in the ED setting, describe its causes, the variability in treatment patterns and characterize the effectiveness and safety of ED standard of care therapies used in the United States.

Methods This is an observational study evaluating the management of hyperkalemia in the ED. Two hundred and three patients who presented to the ED with a potassium value ≥5.5 mmol/L were enrolled in the study at 14 sites across the United States. Patients were treated per standard of care practices at the discretion of the patient’s physician. In patients who received a treatment for hyperkalemia, blood samples were drawn at pre-specified time points and serum potassium values were recorded. The change in potassium over 4 hours and the adverse events after standard of care treatment were analyzed.

Results and Conclusion This article describes the background, rationale, study design, and methodology of the REVEAL-ED (Real World Evidence for Treatment of Hyperkalemia in the Emergency Department) trial, a multicenter, prospective, observational study evaluating contemporary management of patients admitted to the ED with hyperkalemia.

Keywords Hyperkalemia; Potassium; Electrolyte disturbance
INTRODUCTION

Hyperkalemia occurs in up to 10% of hospitalized patients.\(^1\)-\(^4\) Patients with chronic kidney disease and cardiovascular disease, as well as those who are treated with renin-angiotensin-aldosterone system inhibitors, are at greater risk of hyperkalemia.\(^5\),\(^6\) The prevalence of hyperkalemia and related hospitalizations are on the rise in parallel with increased use of renin-angiotensin-aldosterone system inhibitors and an aging hospitalized patient population.\(^7\) Patients are often sent to the emergency department (ED) due to high potassium levels, and over 800,000 hyperkalemia-related ED visits are estimated to occur annually in the US.\(^8\)

If left untreated, hyperkalemia can lead to life-threatening cardiac arrhythmias,\(^9\)-\(^11\) and is associated with substantially increased risk of death.\(^12\)-\(^14\) One study reported in-hospital mortality of patients with hyperkalemia to be as high as 18.1%, while those with normal potassium to be 3.9%.\(^13\) Several other studies have also shown an increase in the risk of death for serum potassium levels above 5 mmol/L and a rapid increase in the risk of death as serum potassium levels exceed 5.5 mmol/L.\(^6\),\(^14\),\(^15\) In particular, a study by Grodzinsky et al.\(^15\) reported that in-hospital mortality was greater than 15% once the maximum potassium level was above 5.5 mmol/L, and another study by Einhorn et al.\(^6\) reported a 1-day mortality rate up to 17 times higher for hospitalized patients with potassium levels > 6.0, as compared to < 5.5 mmol/L.

Although no randomized trials on hyperkalemia treatments and their impact on in-hospital mortality have been conducted, available observational data suggest that reducing potassium levels in patients with hyperkalemia may lower mortality risk. For example, an observational cohort study at two medical centers in Korea found that treatment of patients with hyperkalemia with common therapies excluding dialysis, improved serum potassium levels and had a positive association with better survival.\(^16\) A separate observational study of hospitalized patients who received critical care at two tertiary care hospitals in Boston, MA, showed that a reduction of 1 mmol/L or greater in serum potassium with-

What is already known

Hyperkalemia is frequently encountered in the emergency department and is potentially life threatening. Standard-of-care treatment for hyperkalemia is limited and poorly defined.

What is new in the current study

This is the first prospective, observational study addressing gaps in knowledge in hyperkalemia treatment. This article describes the background, rational and methodology of the REVEAL-ED (Real World Evidence for Treatment of Hyperkalemia in the Emergency Department) trial.

METHODS

Study design

The Real World Evidence for Treatment of Hyperkalemia in the Emergency Department (REVEAL-ED) is a multicenter, prospec-
REVEAL-ED study methods

REVEAL-ED (Real World Evidence for Treatment of Hyperkalemia in the Emergency Department) study sites. Marked areas on the map represent study sites in the US.

tive, observational study evaluating the management of patients admitted to the ED with hyperkalemia. The study was approved by the institutional review board or local ethics committee for each site and registered at ClinicalTrials.gov (NCT02607085). Each patient, legally authorized guardian, or a person with legal responsibility for the patient’s health care decisions provided written informed consent prior to participation in any study activities.

Study setting and population
From October 25, 2015 to March 30, 2016, a total of 203 patients who presented to the ED with a potassium value ≥ 5.5 mmol/L were enrolled in the study at 14 sites across the US (Fig. 1). Eligible patients were ≥ 18 years of age, provided written informed consent, and had hyperkalemia confirmed in the ED with a documented potassium ≥ 5.5 mmol/L. Enrollment of patients with a baseline potassium < 6.0 mmol/L was limited to 50 patients, after which the entry criteria required a baseline potassium ≥ 6.0 mmol/L. A point-of-care analyzer was allowed to determine the baseline potassium level if this was the standard practice at that site. Patients were excluded from the study if, in the opinion of the treating physician, they were unable to perform the tasks associated with the protocol, they were participating in another clinical study which could impact the REVEAL-ED study or they had been previously enrolled in this study.

Study protocol
After patients provided written informed consent, their demographics and medical history data, including previous ED visits and hospital admissions for hyperkalemia, were recorded. Patients with a prior history of heart failure were classified according to the New York Heart Association functional classification system.

The baseline study-related whole blood potassium was deter-
hours after the potassium measurement that qualified the patient for entry into the study if no intervention was performed. Available SOC management data that was recorded included physical examinations, vital signs, fluid intake and urine output, electrocardiograms, clinical laboratory data, and results of chest X-rays. Data regarding the patient’s chief complaint upon ED admission, possible cause of the patient’s hyperkalemia, as well as admitting and discharge diagnoses were recorded. The patient’s overall discharge summary and hospital discharge time were also collected when possible.

The timing of each hyperkalemia intervention following ED admission as well as the dose and route of administration were recorded. Concomitant medications were collected for the 14 days before ED admission through ED discharge. If a patient was admitted to another hospital location (i.e., to an in-patient bed), medications administered after ED evaluation was collected for up to seven days or until discharge from the hospital, whichever came first.

Dates and times were recorded for the following (if applicable): ED admission, hospital admission, intensive care unit admission, observation unit admission, step down unit admission, regular floor admission, discharge (from all admissions), dialysis, do not resuscitate order entry, death, and any other recordable outcome deemed significant by the investigator.

Recordable outcomes were limited to pulmonary edema, ventricular tachycardia/fibrillation, pulseless electrical activity arrest, new clinically significant electrocardiogram changes (specifically including but not limited to severe bradycardia, advanced heart block, bundle branch block, tachycardia [ > 100 bpm]), palpitations, hypoglycemia, and gastrointestinal-related events (e.g., nausea, vomiting, diarrhea) and any other event deemed significant by the investigator. Recordable outcomes requiring positive-pressure ventilation, central venous access, intubation, chest compressions, intravenous (IV) vasoressors, IV vasodilators, IV anti-arrhythmics, and/or emergency dialysis or resulting in death were also collected. These outcomes were recorded from the time of ED admission through ED discharge. If a patient was admitted to another hospital location, post-ED recordable outcomes were collected for up to 7 days following admission to that unit or until hospital discharge, if earlier. Recordable outcomes resulting in death while the patient remained in the hospital were collected for up to 30 days after ED admission.

Outcome measures
The primary endpoint of the study was the absolute change in potassium over 4 hours following the initial intervention for hyperkalemia. If a patient did not receive an intervention for hyperkalemia during the ED admission, then the change over 4 hours following the baseline potassium measurement was used.

Secondary endpoints included the rate of change in potassium over 4 hours following the initial intervention for hyperkalemia, change in potassium at other time points (rate, percent and absolute), choice of intervention, timing and details of procedures relative to ED admission, other outcome events (e.g., hospital and intensive care unit admissions, cardiac arrhythmias and conduction abnormalities, hemodynamic instability/cardiac arrest, inhospital deaths), as well as safety and tolerability of SOC interventions were also evaluated.

Data analysis
No formal sample size calculation was performed for this study. A sample size of 200 patients was selected based on clinical judgement and was considered sufficient to adequately characterize the different interventions in this population. The study populations for analysis include the intent-to-treat and safety populations. The intent-to-treat population included all patients enrolled in the study with any post-baseline study-related potassium values. The safety population included all patients enrolled in the study who had any post-baseline follow-up for safety.

Changes in study-related potassium values following an intervention were used to assess efficacy. All analyses were based on the study-related potassium results obtained using i-STAT. Safety was evaluated using recordable outcomes, clinical laboratory parameters, vital signs, fluid intake and urine output, physical examination, electrocardiograms, and chest X-rays. The principle of treatment emergence was employed for the analysis of recordable outcome data. Treatment emergence was defined to be any event that occurred during the observation period of the study and was not present at baseline, or one that represents an exacerbation of a condition present at baseline.

Recordable outcomes were classified by the medical dictionary for regulatory activities (MedDRA). The type, incidence, timing (onset and duration), relationship to hyperkalemia and to intervention for hyperkalemia, and severity of recordable outcome was reported for treatment-emergent outcomes. Reasons for withdrawal due to recordable outcomes were also reported. The incidence of clinically significant cardiac events (e.g., cardiac arrhythmia, cardiac arrest, cardiovascular and all-cause death) was calculated. All cardiac events were adjudicated by an independent review committee prior to database lock using available SOC data for each case. Descriptive statistics will be presented overall for the study population, as well as stratified by potassium levels at baseline, and by treatment group. When appropriate, hierarchical multivariable analyses will be performed adjusting for differences in patient characteristics and hospital site.
Role of the sponsor
The study sponsor participated in developing the study design, conducted data collection, and will participate in data analyses. The study investigators and all authors provided critical input for the study design and methodology, will have free access to the study data, will lead the analysis and interpretation of the data, and have sole discretion in the writing of the report and the decision to submit the manuscript for publication.

DISCUSSION
Hyperkalemia is frequently encountered in the ED and can lead to cardiac arrhythmias or death. Emergency management of hyperkalemia and close monitoring in the hospital setting is often necessary, but SOC for hyperkalemia has not been well characterized. To our knowledge, this is the first prospective, rigorously designed observational study directly addressing the gaps in knowledge of hyperkalemia management in the United States.

A few noteworthy points about our methodology are as follows: First, our primary end point is to measure the effect of an emergent intervention in the first 4 hours. This time line was chosen to evaluate how quickly the SOC intervention is effective, as severe hyperkalemia can be lethal and quick interventions are needed in the emergency setting. Moreover, this time frame made the study feasible to conduct in the ED setting. Second, we enrolled only fifty patients with a potassium range ≥ 5.5 mmol/L and < 6.0 mmol/L because we wanted to see the effectiveness of the interventions at higher potassium levels. Lastly, even though this was an ED based study and we were interested in the effectiveness of interventions in the first 4 hours, we collected data up to 7 days after admission, when applicable, so we could evaluate some of the lasting side effects of the SOC interventions.

This study has several limitations inherent to the nature of an observational study design. For instance, patients were not randomized to the different interventions since they were treated per SOC practices at the discretion of the patient’s physician. Also, the medications administered as part of SOC practice were not standardized across investigational sites as medications were provided according to the hospital standards at each investigational site. Hence, we expect to find different dosages of the same medication being used at different sites. The observational design of the study allows for an accurate description of the current SOC therapies used to treat hyperkalemia in the US, but the study is not designed to directly compare the efficacy of these interventions.

In summary, the REVEAL-ED study seeks to define the overall burden of hyperkalemia in the ED setting and will describe the variability in treatment patterns as well as characterize the effectiveness and safety of ED SOC therapies used to treat hyperkalemia in the US.

CONFLICT OF INTEREST
No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS
This study was sponsored and funded by ZS Pharma, Jessica Mendoza, PhD, an employee of ZS Pharma provided editorial assistance for the preparation of this manuscript. David Morris of Webb Writes provided statistical support for this study and received consulting fees from ZS Pharma for this work.

REFERENCES


