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Evaluation of the Efficacy of an Intravenous Potassium Repletion Algorithm in Trauma Intensive Care Patients

Lee Anne Chittom

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Lee A. Chittom

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Abstract

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Low serum potassium, medically known as hypokalemia, is a common phenomenon in patients sustaining traumatic injuries and head trauma. Maintenance of potassium homeostasis is imperative to improve outcomes for trauma patients. Mortality risk increases with severe hypokalemia, defined as serum potassium levels less than 2.5 milliequivalents/deciliter (mEq/dL) (1). It appears there are other variables which affect serum potassium levels in the presence of mild hypokalemia which may provide the clinician with a difficult task of achieving desired serum potassium levels of 4.0 mEq/dL. Variables may include physiological homeostasis, depletion in total body potassium stores and other unknown factors. Recommendations for repletion of serum potassium levels in critically ill hospitalized patients is in increments of 10 mEq potassium chloride (KCL) per hour up to 20 mEq KCL per hour and in severe situations with electrocardiograph changes up to 40 mEq KCL per hour intravenously (2).

The nutrition support service at The Regional Medical Center at Memphis has been utilizing an empiric algorithm for potassium repletion for the treatment of hypokalemia in the Elvis Presley Memorial Trauma Center patients requiring specialized nutrition support. The purpose of this research is to evaluate the efficacy of this potassium repletion algorithm. Treatment of hypokalemia is important in critical illness for maintaining proper cardiac function as well as prevention of muscle paralysis, arrhythmias and other complications.

Patients with moderate to severe hypokalemia showed a greater improvement in serum potassium levels upon receipt of sixty mEq or eighty mEq KCL. Although the study groups were small for both the moderate to severe hypokalemia groups there was statistical significance with both treatment groups. The results in the moderate to severe hypokalemia groups can be attributed to lower total body potassium stores and increased need for exogenous potassium.

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CHAPTER 1

REVIEW OF LITERATURE

Introduction

Low serum potassium, medically termed hypokalemia, is a common phenomenon in patients sustaining traumatic injuries. Mortality risk increases with severe hypokalemia, considered to be serum potassium levels less than 2.5 milliequivalents per deciliter (mEq/dL) (1). Recommendations for repletion of serum potassium levels in critically ill hospitalized patients is dosed in increments of 10 mEq potassium chloride (KCL) per hour up to 20 mEq KCL per hour and in severe situations with electrocardiograph changes up to 40 mEq KCL per hour intravenously (2). Maintenance of potassium homeostasis is imperative to improved outcomes for trauma patients.

The nutrition support service at The Regional Medical Center at Memphis has been utilizing an empiric algorithm for potassium repletion for the treatment of hypokalemia in the Elvis Presley Memorial Trauma Center patients requiring specialized nutrition support. The purpose of this research is to evaluate the efficacy of this potassium repletion algorithm (Table1).

Role of Potassium in the Body

Potassium plays an important role in cardiac and muscle function. It is found in both intracellular and extracellular fluid with 98 percent of total body potassium found in intracellular volume, making it a major intracellular cation. A delicate balance occurs between the intracellular and extracellular fluid compartments; very small shifts can have a large impact on total plasma levels. Extracellular potassium concentration impacts

balance in two ways is total body potassium content and relative distribution of potassium to intracellular and extracellular fluid compartments.

The first way is total body potassium content is determined by the difference between potassium intake and excretion. Equilibrium occurs when the amount of potassium ingested equals the amount excreted. Intake varies according to diet but the kidneys handle 90% of output while the rest is excreted into bowel and is eliminated in feces. Upon ingestion, potassium is quickly absorbed and moved into circulation via portal circulation. Once in portal circulation, potassium stimulates secretion of insulin which acts on the Na-K-ATPase pump to facilitate the entry of potassium into cells (3).

A secondary mechanism for maintenance of intracellular potassium balance is distribution of potassium between organs and extracellular tissue. This distribution is regulated by many hormones and acid-base balance and tonicity of plasma. On the other hand, an enzyme located in the cell membrane allows potassium to move against an electrical gradient and pumps potassium out of the cell in exchange for sodium. In steady state, the rate of active potassium transport into the cell is equal to the rate of passive diffusion of potassium out of the cell (4).

Imbalances in potassium levels can have profound effects on patients. Hyperkalemia, considered to be serum potassium of > 5 mEq/dL, can have a catastrophic effect on the human body. Serious consequences of hyperkalemia include impaired cardiac function with arrhythmias, peaking Terahertz radiation (T waves) and widening of series of wave forms: negative Q wave before positive R wave followed by the S wave by negative deflection after an R wave on electrocardiogram (QRS complex).

Paralysis occurs once serum potassium levels consistently reach greater than 7.5mEq/dL (3).

Hemolysis is a common cause of hyperkalemia. Pseudo-hyperkalemia results from improper blood specimen collection, transport or in processing the specimen. When this happens, patients are treated for a false diagnosis of hyperkalemia.

Acid-base disturbances are associated with hyperkalemia, primarily acidosis. In the presence of acidosis, potassium ions are pushed out of the cells due to intracellular influx of hydrogen ions. Acidosis increases serum potassium due to pushing potassium out of the cell to maintain electrical balance. Alkalosis decreases serum potassium by pushing potassium back into the cell and increasing urinary potassium excretion. A common rule of thumb to determine the inverse relationship between potassium and pH is every 0.1 drop in pH results in a 0.6 rise in potassium. However, a more accurate description of the change in serum potassium is a 0.4 to 1.3 mEq/L for every 0.1 change in pH (4,5).

Other causes of hyperkalemia are acute or chronic kidney disease (CKD), diabetes (DM), advanced age, and medications which may perpetuate elevations in serum potassium (6). In kidney disease, secretion is decreased due to diminishing renal cell mass; unfortunately, this process is further complicated as the renal function worsens limiting amounts of potassium secreted. Hyperkalemia in diabetics is related to reduction in insulin or lack of insulin production which prohibits potassium movement into cells. Primarily this occurs in diabetics with poorly managed disease or increased insulin resistance resulting in prolonged hyperglycemia which leads to impaired renal

function. As a person ages, normal organ function is reduced; and medications can exacerbate the effects on potassium balance.

Medications cause hyperkalemia by impairing secretion of potassium or increasing the level of potassium in the body. Potassium sparing diuretics such as spironolactone or triamterence inhibit renal potassium excretion. Potassium containing antibiotics such as penicillin-G potassium (Pen-G K) provide 1.68 mEq per million units of potassium. Initially this quantity of potassium appears small; however, a patient may receive 32 mEq to 160 mEq potassium over twenty-four hours which could cause hyperkalemia (7,3).

Other classes of medications which impact potassium balance include agiontensin-converting enzyme inhibitors (ACEI), non-steroidal anti-inflammatory drugs (NSAIDS) and heparin. Angiotensin-converting enzyme inhibitors reduce aldosterone levels in individuals with both normal and impaired renal function. Therefore, potassium intake should be monitored routinely to ensure serum levels do not become elevated. Nonsteriodal anti-inflammatory drugs (NSAIDS) suppress renin and aldosterone secretion by inhibiting prostaglandin synthesis (3). Renal blood flow is reduced and prostaglandin synthesis is decreased, which affects synthesis of aldosterone thus causing hyperkalemia. Heparin can induce hyperkalemia due to suppression of aldosterone and reduction in affinity of angiotensin II receptors in the adrenal gland. Hyperkalemia is a rare side effect of heparin occurring after several days of therapy; usually in those persons with underlying renal impairment or diabetes (7).

Although hyperkalemia can have deadly results, hypokalemia is just as detrimental especially since it is more common than hyperkalemia. Most laboratories

would consider potassium of 3.5-5.0 mEq/dL normal. However, symptoms of hypokalemia may not manifest until serum potassium is <2.5mEq/dL. The most common complications of hypokalemia include muscle paralysis, arrhythmias, gastrointestinal ileus, and rhabdomyolysis. Most significantly, cardiac death can occur if hypokalemia is severe enough or left untreated (2,3,4).

There are many factors which may contribute to hypokalemia. The most common factors are increased losses of potassium through the kidney and gastrointestinal tract. Secondary causes are related to rapid influx of potassium into the cell during use of insulin infusions, a sudden rise in pH, or metabolic alkalosis related to gastrointestinal losses, or decreased renal perfusion from hypovolemia or heart failure. Tertiary causes include hypomagnesemia, theophylline toxicity, delirium tremens, and digitalis toxicity (3).

Potassium and Trauma Patients

In trauma patients, hypokalemia has resulted from beta adrenergic stimulation of the sodium-potassium adenosine triphosphatase pump (Na-K-ATPase) due to large release of catecholamines after an injury. The incidence of hypokalemia in trauma patients is 50 to 68 %. The greater the number of organ systems injured; the higher incidence of hypokalemia and increased mortality (1). Hypokalemia is also a result of increased gastrointestinal losses and increased blood loss from trauma and surgery.

Initially, critical care specialists believed that hypokalemia occurs upon initial injury but normalized within the first twenty-four hours of critical care without requiring potassium repletion. In patients with blunt, penetrating abdominal trauma, or liver injuries, it has been suggested that potassium losses are a result of β-adrenergic stimulus

both pre-operatively and post-operatively (8). Similar suggestions have also been made for those patients with traumatic brain injury (TBI) (9). Hypokalemia may also relate to age, arterial pH and serum catecholamine levels (6).

Researchers challenged the theory of early hypokalemia, finding symptoms occur beyond the initial admission and continuing longer than the first forty-eight hours of admission into the hospital (9). It is suggested, that hypokalemia is not resultant of administration of potassium containing intravenous fluids or blood products (10). Trauma patients sustaining TBI have a greater incidence of hypokalemia occurring beyond the first twenty-four hours of admission and continue more than one week after injury. Those patients with TBI not only required more potassium, but also remained hypokalemic longer in comparison with their non-traumatic brain injured counter parts (9).

Pampolini investigated the incidence of hypokalemia in pre-operative and post operative abdominal trauma patients (8). Plasma potassium, sodium, calcium, and chloride were evaluated before and after surgery in 123 patients with injuries consisting of hepatic trauma (n=16), spontaneous liver rupture (n=3), extra hepatic trauma: spleen (n=23), mesentery (n=12), multiple trauma (n=12), ruptured abdominal aortic aneurism (n=8), hepatic resection (n=19), extrahepatic abdominal organs in patients presenting some abnormalities in liver function (n=15) and diagnostic laporatomy (n=15). These patients were matched with non-traumatically injured patients with ages ranging from 4 to 64 years. Results from the study revealed 15 out of 16 patients with hepatic trauma had normal serum potassium pre-operatively, but sustained drastic decreases in serum potassium post-operatively ($p<0.001$). There were no significant differences in plasma

sodium, calcium, and chloride levels between pre-operatively and post-operatively. Plasma potassium levels continued to fall dramatically in those patients who underwent hepatic resection. Additionally, serum glucose levels remained normal to upper limits of normal, and blood pH levels were also stable. Thus the investigators hypothesized that hypokalemia could not be attributed to a bowel wasting of the cation or to urinary losses due to frequent reduction in urine output due to hypotension. However, according to Pampolini results couldn't be completely quantified due to need for surgery or other procedures which impeded 24-hour urine collection for potassium content.

Pampolini concluded hypokalemia could be attributed to shift in potassium from the blood stream into the intracellular space. Plasma chloride levels and pH were reported as normal. The investigators suggested that reasons for the presence of hypokalemia following hepatic vs. abdominal injuries were intrinsically related to the liver as it contains greater amounts of adrenergic endings. Epinephrine is known to lower serum potassium levels via stimulation of beta-adrenoceptors, which induce the uptake of potassium by the liver and skeletal muscle. The authors in this study inferred the norepinephrine released by the liver acts with a similar mechanism. It was noted that the potency of norepinephrine is less than epinephrine; when large amounts of norepinephrine are released locally, the scarce receptor affinity can be overwhelmed so that epinephrine-like effects result. Most of the norepinephrine release occurs locally so a majority of hypokalemia is related to uptake by the liver due to the large size of this organ. The persistence of hypokalemia goes beyond the short half- life of norepinephrine and may be explained by an increase in plasma aldosterone. In addition to raising urinary excretion of potassium, aldosterone also enhances the shift of potassium from the

blood into the cells. The increase in plasma aldosterone levels is a consequence of enhanced rennin release due to adrenergic stimulation and possibly a selective impairment of the hepatic metabolism of the hormone, due to accidental or surgical injury to the liver. Investigators ruled out insulin as a contributor of hypokalemia for multiple reasons. Norepinephrine inhibits release of insulin; higher than normal levels of plasma insulin are needed to shift blood potassium into the intracellular space and the hepatic neurogenic contribution to glycogenolysis is poor and the consequences are small. Additionally if insulin is released in response to the intra- and/or postoperatively infused glucose, an overlapping hypokalemia should be observed in patients undergoing extrahepatic abdominal operations or diagnostic laporatomy. In summary, the authors stated the incidence of hypokalemia in pre-operative and postoperative abdominal trauma patients gave rise to the following considerations. It is mandatory to serially and frequently control hypokalemia to reduce risk of onset of dangerous arrhythmia especially in patients receiving digoxin. In 20-30 percent of cases of liver trauma, the clinical picture is blurred; a mild pain at the upper right abdomen associated with hypokalemia may be indicative of a lesion on the liver (8). Early accurate diagnosis is imperative in order avoid hypokalemia.

More recently Vanek et al. studied the pathophysiology of changes in serum potassium levels in trauma patients (11). The study consisted of 133 trauma patients, ages 2-88 years in the study group; 59 patients were enrolled in the control group with ages ranging from 16- 87 years. Most of the study participants and control participants were males; only 30 patients in the study were female with 9 female patients in the control group. Traumatic injuries consisted of blunt and penetrating trauma with the

number of systems injured ranging from one to three systems. Variables recorded upon admission to emergency room (ER) were systolic blood pressure (SBP), Champion trauma score, arterial pH, spot urine for potassium and serum potassium (K1), glucose, alcohol, and catecholamine levels. About 24 hours after admission, spot urine potassium and serum potassium (K2) and catecholamine levels were recorded as well as the approximate amount of potassium given during the first 24 hours after admission. Other variables recorded were age, sex, mechanism of injuries, organ systems injured, lowest SBP, estimated blood loss (EBL) in the first 24 hours of injury and Injury Severity Score (ISS). Patients in the control group were selected based upon admission for elective inguinal hernia repair as these patients were predominantly male and had serum potassium levels measured as a part of routine preoperative evaluation. Patients excluded were those with burn injuries, patients receiving diuretic therapy or medications that can affect serum potassium levels and those patients with hemolyzed blood specimens. The group differences were expressed in t tests and chi-square tests. The association of serum potassium and putative risk factors were assessed using t tests and Pearson's correlation coefficients. Least squares multiple regressions was used to identify the subset of variables that best predicted serum potassium while controlling potential cofounding between the independent variables in the model (11).

Results of the Vanek study revealed there was no significant difference between the two groups; however, the control group was significantly older than the study group. The study group had a lower mean K1 (3.55 ± 0.44 vs. 3.95 ± 0.34) and higher incidence of hypokalemia (50% versus 10%) than the control group. Hypokalemia was defined as serum $K<3.6$ mEq/L. The difference between the group's serum potassium levels

persisted when they were broken down by age. K1, K2, and approximate amount of potassium administered in the first 24 hours were recorded in 91 patients. The mean K1 was 3.56 ± 0.53 mEq/L, and the incidence of hypokalemia was 47%. K2 was drawn approximately 24 hours later averaging 4.03 ± 0.39 mEq/L, and the incidence of hypokalemia was only 9%. Both K2 and incidence of hypokalemia at 24 hours differed significantly from initial levels and were similar to the control group's values. The authors used a standard nomogram to predict total body potassium content based on serum potassium and pH. Approximately 204 mEq of potassium is necessary to increase serum potassium from 3.6 to 4.0mEq/L. However, the mean amount of potassium given to this subgroup was only 38 ± 37 mEq. There was no statistical difference in the serum catecholamine levels of the study group (11).

In conclusion, the Vanek study found that hypokalemia was significantly more common in trauma patients with an incidence of 50% of study subjects and only 10% of control subjects. Although the reason was unclear to the authors, they alluded to the fact that the change in serum potassium levels occur frequently. Hyperkalemia is believed to be less common in trauma patients as confirmed in Vanek et al study. Hyperkalemia is typically seen in cases of shock, hypo-perfusion and acidosis due to the extracellular shift of potassium. However, it should be noted that low systolic blood pressure did not correlate with serum potassium levels. In addition, the results yielded conflicting relationships between the arterial pH, admitting SBP, and TS with initial serum potassium levels. Soft tissue injury followed by the release of potassium from damaged cells is a factor in hyperkalemia. Researchers found this factor to have no significant difference between patients with or without musculoskeletal injuries. Nevertheless,

hypokalemia occurs quickly and resolves just as rapidly as incurrence of injury. Vanek et al. did validate previous data reporting the incidence of hypokalemia occurring in more than 50% of trauma patients and that this phenomenon was more common than hyperkalemia. It was also noted upon reviewing incidence of hypokalemia based upon organ systems that there was no significant difference in their patient population despite the fact that 60% of their patients were admitted with multiple organ systems injury. While the actual cause of hypokalemia in trauma patients remains unknown, it appears to be related to an intracellular shift of potassium. This conclusion is supported by the rapid onset and resolution of serum potassium levels without significant exogenous potassium replacement. Thus, it appears hypokalemia in trauma patients occurs due to multiple factors; however, the exact mechanism remains unclear (11).

Studies of Potassium Repletion in Trauma Patients

In order to maintain optimal potassium balance in hospitalized patients, a study conducted by Kruse and colleagues evaluated the optimal tolerance of short-term intravenous potassium infusions up to 40 mEq potassium chloride (KCL) per hour (13). This study showed that repletion via central or peripheral infusion sets was acceptable with caution that phlebitis may occur with peripheral administration (13). Kruse's study looked at effects of individual short term potassium infusion sets at a rate 20 mEq/hour. 1463 infusions were reviewed, 111 were excluded due to the fact that post-infusion potassium levels were obtained outside 12 hours of infusion. Consequently, a total of 1351 infusions were reviewed. The total number of patients in the study was 190; all were admitted to the intensive care unit due to medical illnesses ranging from respiratory failure, shock, renal failure, diabetic ketoacidosis, heart failure, and other medical

illnesses. Mean pre-infusion potassium was 3.2 mEq/L with average post infusion potassium 3.8 mEq/L. There were 10 instances of hyperkalemia defined by the study as serum potassium levels of 5.3 to 6 mEq/L. All potassium was given intravenously with no documented changes in electrocardiographs (ECG). Kruse recommended dosing short term intravenous potassium via central or peripheral routes at rates of 20 mEq/ hour in the intensive care setting but cautioned that cardiac monitoring should be used (13).

Additionally, Kruse evaluated short term intravenous infusions of 20 mEq potassium chloride in 100 ml normal saline over one hour (14). Forty patients were enrolled in the study, 19 female and 21 male with a mean age of 59 years. Exclusion criteria were those patients already receiving enteral or parenteral nutrition, antiarrhythmic drugs, and diuretics, catecholamines, or sodium bicarbonate. Monitoring was conducted for electrocardiographs (ECG); one hour before potassium infusion and again during the infusion of potassium. Serum potassium levels were obtained in 15 minute intervals upon initiation of the potassium infusion as well as 45 minutes post infusion via arterial catheters. Mean plasma potassium was 2.9 mEq/L at baseline; all other serum values varied from baseline post infusion by ANOVA ($P < 0.001$) and Dunnett's test ($P < 0.001$). Peak potassium was 3.5 mEq/L with mean post infusion change in potassium 0.48 mEq/L. Average change in pH was 0.01 ± 0.005. Cardiac rhythm showed normal sinus rhythm in 29 patients, atrial fibrillation in two patients and multifocal atrial tachycardia in one patient. There were no significant changes in ECG from baseline to infusion; however, the frequency of premature ventricular complexes (PVCs) decreased during infusion. The authors concluded the infusion of 20 mEq KCL over an hour is safe for patients with peak potassium levels climbing towards the

midpoint or two thirds from completion of the infusion; however, levels dropped back down very rapidly upon completion. Kruse hypothesized that this drop is due to homeostatic mechanism, but there was no evidence of hyperkalemia post-infusion. The researchers didn't allude to the fact that the patients entered into this study had significant hypokalemia; thus, one would anticipate an infusion of 20 mEq KCL per hour to be acceptable evidenced by the serum potassium level falling back down towards low normal ranges of serum potassium 3.5mEq/L. The authors provided evidence regarding improvement of PVCs which is symptomatic of severe hypokalemia; therefore, the data presented would lead one to believe infusing 20mEq KCL over one hour would be an acceptable practice (14).

Hamill completed a small study consisting of 48 patients in the intensive care unit, ages 29 to 86 years, concentrating on the safety and efficacy of short term intravenous potassium infusions (2). The criteria for admittance in the study was serum potassium of < 3.5mEq/L. Primary diagnosis to the intensive care unit was postoperative cardiac surgery (n=9), sepsis and multiple organ system failure (n=9), complicated myocardial infarction (n=7) and respiratory failure (n=5). Potassium infusion interventions were provided in increments of 20mEq, 30mEq, and 40 mEq in 100 ml normal saline infused over one hour and were administered to patients for serum potassium levels of <3.2 but >3.2 mmol/L (n=26), 3.0 to 3.2 mmol/L (n=11, and <3 mmol/L (n=11). Urine and serum potassium were collected during infusion and one hour post infusion. All patients tolerated infusions without evidence of ECG changes or new dysrhythmia requiring intervention. The mean highest potassium level achieved was 0.5 ± 0.3 mEq/L, 0.9 ± 0.4 mEq/L and 1.1 ± 0.4 mEq/L in the 20 mEq, 30 mEq, and 40 mEq

groups respectively with maximum serum potassium levels at the completion of infusion. These results were statistically significant ($p < 0.5$). Urinary potassium excretion was increased in all groups during infusion but most significantly in the 30 mEq and 40 mEq infusion groups respectively. The authors concluded all three dosing schemes were safe over a one hour infusion time. However, they noted that long-term efficacy of the potassium received was not studied. This patient population was somewhat similar to trauma patients; but unfortunately as it pertains to this research, patients were primarily medical intensive care patients (2).

A more recent study reviewing the influence of traumatic brain injury (TBI) on serum potassium and phosphorus homeostasis in critically ill multiple trauma patients was conducted to ascertain if TBI patients require more aggressive repletion of potassium and phosphorus(9). For the discussion of this review, the results of potassium infusion were examined. The researchers studied 50 patients; 25 multiple trauma patients and 25 TBI patients receiving mechanical ventilation without renal impairment who were admitted into the trauma intensive care unit or to the neurotrauma intensive care unit for the first 14 days of admission. The TBI patients' mean age was 33 ± 12 years compared with trauma patients without TBI 42 ± 17 years. Additionally, the TBI patients had a lower weight 79 kg ± 16 versus 94 kg ± 27. The admission Glasgow Coma scale was 6 ± 2 TBI versus 10 ± 4 in patients without TBI. Injury Severity Scores (ISS) in those patients with TBI were higher, 33 ± 2 versus 29 ± 2 in those non-TBI patients. Target serum potassium concentration was 4 mEq/dL. Although they had a greater mean potassium intake, serum potassium levels were consistently lower in the TBI patients ($P < 0.001$). Hypokalemia was defined as serum potassium <3.5 mg/dL with short term

potassium infusion dosing for serum levels of 3.5 to 3.9 give 40 mEq KCL, 3 to 3.4 give 80 mEq KCL, and <3 give 120 mEq KCL. Even though TBI patients received more than twice the amount of potassium of non-TBI patients their mean serum potassium concentrations never reached goal potassium level 4 mEq/dL. On the contrary more than 50 % of the non-TBI patients achieved target serum potassium ($P < 0.002$). The study suggested that further investigation should be conducted to determine if more aggressive dosing of potassium is warranted in these patients (9).

Hypokalemia in trauma patients is very common due to severity of injury, lower systolic blood pressure, and intracellular cation shifts with normal renal potassium excretion. Incidence of hypokalemia occurs in greater than half of trauma patients (5). Low potassium can be attributed to tachycardia and decreased myocardial contraction as a result of increase stimulation of beta 2-adrenergic receptors by catecholamine. It has recently been found those trauma patients with TBI require two times the amount of potassium for the treatment of hypokalemia. In a study by Lindsey et al., non-TBI trauma patients achieved potassium homeostasis within the first week of therapy; however, the TBI patient required additional aggressive potassium therapy for greater than two weeks without achieving targeted serum potassium of 4.0mEq/L (9). Studies have reflected the benefits of normalizing potassium levels. There have been suggestions as to how much potassium to give at a single short-term infusion and acceptable routes of delivery either oral or intravenous. There is a need to investigate efficacy of potassium dosing schemes or algorithms used to replace serum potassium levels and to determine if desired results are achieved.

The purpose of this study was to determine the efficacy of the short term intravenous dosing algorithm used by the nutrition support service at the Regional Medical Center at Memphis for trauma patients requiring specialized nutrition support who are admitted to the Elvis Presley Memorial Trauma Center. The goal was to achieve serum potassium of 4.0mEq/L utilizing potassium short term infusion guidelines of the nutrition support service. The dosing algorithm is mild hypokalemia or serum potassium 3.5 -3.9 mEq/L give 40mEq potassium, moderate hypokalemia or serum potassium >3-3.4 mEq/L give 60 mEq potassium, and for severe hypokalemia or serum potassium <3 mEq/L give 80 mEq potassium.

CHAPTER 2

METHODS

Subjects

This study is a retrospective chart review of 57 patients admitted to Elvis Presley Memorial Trauma Center between February 2008 and February 2011. Inclusion criteria are those patients between the ages of 18 and 65 years requiring specialized nutrition support for greater than seven days. Patients without acute kidney injury, defined as serum Creatinine <2mg/dL, as those with acute or chronic kidney injury require lower potassium dosing. Other patient demographics collected included Glasgow Coma Scale (GCS), arterial pH, admitting white blood cell count (WBC), admitting cortisol levels as well as serum albumin, serum pre-albumin, admitting lactate and amounts and frequency of as well as amounts of packed red blood cells (PRBC). Lastly, serum glucose levels and finger stick glucose levels were recorded as well as the quantity of insulin received.

Patients were excluded if they had a history of taking or were taking scheduled medications which are known to significantly alter potassium homeostasis. These medications include diuretics, angiotensin-converting enzyme inhibitors, beta-2 agonists, octreotide or oral calcium supplementation, angiotensin-II receptor blockers, trimethoprim, continuous heparin infusion, nonsteroidial anti-inflammatory agents, or amphotericin B. Additionally, exclusion criteria included those patients admitted under the age of 18 or over the age of 65 years, those with thermal injury or HIV/ AIDS.

Procedure

Pre-infusion serum potassium levels were recorded on patients in the study, as well as pH, serum glucose, blood urea nitrogen (BUN), serum creatinine, serum magnesium, and quantity of magnesium received if infusion required. Evaluation of post infusion potassium levels were recorded to determine positive or negative response to the quantity of potassium received. Additional data collected included intake and output volumes on enteral and/or parenteral volume received, volumes of nasogastric output, and stool volumes when diarrhea was present. Medications to be evaluated due to the potential effect on serum potassium levels included insulin, such as regular human insulin utilized for short term glucose management as well as intravenous regular human insulin infusion volumes, and intermediate or long term insulin administration.

Statistical Analysis

Three analysis of variance tests (ANOVA) were conducted using Sigma Plot version 11.2 for Windows. Data analyzed were dose responses to 40 mEq, 60 mEq and 80 mEq KCL based upon dose per kilogram body weight, change in potassium (K) with $p = < 0.050$. Linear regression was also utilized to determine the relationship between K dose and change in serum K.

CHAPTER 3

RESULTS

The population demographics for all three groups were very similar, in age, sex, BMI and mode of injury. Group one was larger in number of patients (n=40) and more patients who were male (n=35) (Table 2). The larger number of male subjects to female subjects in trauma patients is not uncommon; it is typically males with more physically demanding jobs and usually to participate in more high risk activities. Groups two and three only contained 8 patients each; both were also evenly distributed male to female patients (Table 4, 5). The patients in group three were slightly younger and slightly lower weight than previous two groups but not significant to study.

The treatment of mild hypokalemia using a single short term infusion dose of 40 mEq KCL resulted in no significant or statistical changes in serum potassium levels (Table 3). Pre-infusion serum potassium levels were 3.7 ±0.26 standard deviations with post infusion level 3.7 ± 0.36 with a 95% confidence interval. The group was large enough (n=41) to reflect any variables in the sample. There was no change observed between the subjects' weight, serum potassium level and dose of intravenous potassium provided.

For the second treatment group with moderate hypokalemia (n= 8), patient demographic were similar to group one more male and female patients (Table 4). The patients weighed the same and they were similar in race. Serum potassium levels were lower which supported a higher dose of KCL. There was a clinically significant response to a short term infusion of 60 mEq KCL with p = 0.163. Potassium response

to 60 mEq potassium dose resulted in a clinically relevant increase in potassium (Table 3). This increase was statistically significant with 95% confidence interval for difference of means 0.591 to 0.0657. The findings indicated a 0.26 point rise in serum potassium after administration of 60 mEq KCL dose. This rise could be due to chance related to the small study group; however, it cannot not be ruled out as actual response to short term infusion of potassium chloride due to the positive response.

The final treatment group of 80 mEq potassium chloride dose (n=8) these patients were slightly younger than the previous two groups and lower weight (Table 4). Their serum potassium level was much lower than previous which justified the dose of potassium administered. For the treatment of moderate to severe hypokalemia achieved statistical significance (p= 0.467) with 95% confidence interval for difference of means 1.110 to 0.05153 (Table 4). Although the study group was small (n=8), the response to the short term infusion reflected a rise in serum potassium by 0.6 mEq/dL. Thus, the response to 80 mEq KCL short-term infusions is greater than what would be expected by chance (p= 0.045).

CHAPTER 4

DISCUSSION

In group one treatment of mild hypokalemia, it appears that 40 mill-equivalents (mEq) potassium chloride does not make a significant impact towards achieving target serum potassium levels of 4.0 mEq/dL based upon mean pre-infusion potassium levels 3.6 ±0.2 mEq/dL standard deviations. Post infusion potassium levels were 3.7 ±0.4 mEq/dL standard deviations. The difference between the two groups was 0.07 with a confidence interval 0.189 to 0.0474. The 40 mEq KCL group did not reflect change in serum potassium ($p<0.50$). The limited response may be reflective of physiological variables to maintain homeostasis. The treatment group failed to show a significant change in serum potassium $p= 0.233$ target $p< 0.050$; therefore it cannot be ruled out the change was due to chance. The population size did not contribute to failure of the results in this study group.

In group two, moderate hypokalemia, the mean pre-treatment serum potassium levels were 3.5 ± 0.2 standard deviations and post treatment serum potassium levels of 3.8 ± 0.3 standard deviations. The difference between the two groups was 0.263 with seven degrees of freedom. The population was small, containing only 8 patients; however, providing a short term infusion of 60 mEq KCL proved beneficial in treatment of moderate hypokalemia ($p= 0.163$) and 95% confidence interval. The change that occurred with the treatment is not great enough to exclude the possibility that the difference is due to chance. 60 mEq KCL short term infusion appears to be advantageous in improving serum potassium levels.

The most significant improvement in serum potassium levels via short term infusion was found in the severe hypokalemia group three with serum potassium levels <3.5 mEq/dL. Mean pre-infusion potassium was 3.3 mEq/dL ± 0.1 standard deviations and mean post infusion potassium level 3.9 mEq/dL ± 0.6 standard deviations. This treatment group had statistical significance (p=0.467). The difference was 0.563 with 95 percent confidence interval and seven degrees of freedom (p=0.045). The change which occurred with the treatment achieved desired result is greater than would be expected as evidenced by p=0.045.

Further analysis was conducted comparing each dosing regimen to the next; however, this analysis failed to pass (p<0.050) but passed equal variance test (p=0.423). Upon comparing 40 mEq KCL dose (group 1) to 80 mEq KCL dose (group 3), the difference between the means was 0.492 with p= 0.011. When compared between the 60 mEq KCL dose (group 2) to 80 mEq KCL dose, there was no difference between the two groups (P<0.050). Similarly, when group 1 was compared to group 2, there was no difference between the two groups (p<0.050). The difference between the mean values among the treatment groups one and three are greater than would be expected by chance resulting in a statistically significant difference (p=0.031).

The treatment of hypokalemia is important in critical illness for maintaining proper cardiac function as well as prevention of muscle paralysis, arrhythmias and other complications. It appears there are several variables which affect serum potassium levels in the presence of mild hypokalemia which may provide the clinician with a difficult task of achieving serum potassium levels of 4.0. These variables may include physiological homeostasis, less depletion in total body potassium stores and other unknown factors.

The results of the study indicated that there is benefit to higher potassium dosing for the treatment of moderate to severe hypokalemia as reflected in the results showing greater improvement in overall serum potassium levels. Although the study groups were small for both the moderate to severe hypokalemia groups, there was statistical significance for higher potassium chloride dosing with both treatment groups. The results in the moderate to severe hypokalemia groups can be attributed to lower total body potassium stores and increased need for exogenous potassium.

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GLOSSARY

1. Arrhythmias: Irregular heartbeats, caused by cardio vascular disease, electrolyte disturbances: sodium and potassium, changes in heart muscle or heart attack such as premature ventricular contractions (PVCs), atrial fibrillation, premature atrial contraction, prolonged QT syndrome and tachycardia.
2. Exogenous: introduced from or produced outside the organism or system
3. Homeostasis: a normal state of balanced and stable internal environment, which can vary slightly to accommodate external changes.
4. Empiric: Pertaining to a method of treating disease based on observations and experience without an understanding of the cause or mechanism of the disorder or the way the therapeutic agent or procedure affects improvement or cure.
5. Plasma: Liquid portion of blood; contains water, proteins, salts, nutrients, hormones, and vitamins
6. Portal Circulation: circulation of blood through larger vessels from the capillaries of one organ to those of another; applied to the passage of blood from the gastrointestinal tract and spleen through the portal vein of the liver.
7. Na-K-ATPase pump: Sodium-Potassium-Adenosine triphosphatase pump: a complex in the plasma membrane catalyzing the approximate reaction ($Na^+ + K^+$) - ATPase and Na^+, K^+ ATPase. Sodium and potassium concentrations in cells are maintained by pumping Na out of the cells and K into cells (against their concentration gradients) at the expense of ATP hydrolysis.

8. Acid-base balance: A means of maintaining balance between hydrogen ions within the body.
9. Tonicity: State of tissue tone or tension, or the effective osmotic pressure equivalent.
10. Electrical gradient: a measure of electrical change over a specific quantity
11. Influx: Act of flowing in
12. pH: the symbol relating the hydrogen ion concentration or activity of a solution to that of a given standard solutions. pH is approximately equal to the negative logarithm of hydrogen concentration expressed in molarity.
13. Aldosterone: main mineralocorticoid hormone secreted by the adrenal cortex, the principle biological activity of which is the regulation of electrolyte and water balance by promoting the renal retention of sodium and the excretion of potassium.
14. Angiotensin: a polypeptide present in the blood and formed by the catalytic action of renin on angiontensinogen in the blood plasma.
15. Angiotensin-II: an octapeptide hormone, powerful vasopressor and stimulator of aldosterone secretion by restricting pressure and diminishes fluid loss in the kidney by restricting flow.
16. Gastrointestinal ileus: Obstruction of the intestines
17. Rhabdomyolysis: disintegration or dissolution of muscle, associated with excretion of Myoglobin in the urine.

18. Metabolic alkalosis: a disturbance in which the acid-base status of the body shifts toward the alkaline side because of retention of base or loss of noncarbonic or nonvolatile acids.
19. Delirium tremens: an acute, reversible organic mental disorder characterized by reduced ability to maintain attention to external stimuli and disorganized thinking as manifested by rambling, irrelevant, or incoherent speech; tremens caused by cessation or reduction in alcohol consumption, typically in alcoholics with 10 or more years of heavy drinking. Clinical symptoms: tachycardia, sweating, and hypertention, a coarse irregular tremor and delusions, vivid hallucinations, and wild agitated behavior.
20. Beta-adrenergic stimulaton: Stimulation of G-proteins such as epinephrine and norepinephrine, to stimulate sodium uptake by the kidney during fight or flight response.
21. Glycognolysis: break down of glycogen to glucose by hydrolysis (digestion or within lysosomes) or phosphorolysis (mobilization of glycogen as fuel).
22. Champion Trauma Score: A physiological scoring system, with high inter-rater reliability and demonstrated accuracy in predicting death, scored from the first set of date gathered on a patient admitted due to traumatic insult. It consists of Glasgow Coma Scale, Systolic Blood Pressure, and Respiratory rate.
23. Injury Severity Score: anatomical scoring system that provides an overall score for patients with multiple injuries. Each injury is assigned a score and is allocated to one of six body regions (head, face, chest, abdomen, extremities, and external). Only the highest score from each region is used. Three of the most severely

injured body systems have their score squared and added together to produce the ISS.

24. Phlebitis: Inflammation of a vein; a condition is marked by infiltration of the coats of the vein and the formation of a thrombus.
25. Diabetic Ketoacidosis: acidosis accompanied of ketone bodies in the body tissues and fluids, specifically when glucoses are extremely elevated due to poorly controlled diabetes or new onset of diabetes.

APPENDIX A

Table 1. Nutrition Support Service potassium repletion algorithm

These doses should NOT be used patients with renal impairment or adrenal insufficiency.

Serum K (mEq/L)	KCL Dosage (mEq)	Laboratory work
3.5 – 3.9	40 mEq X 1; increase in IV's/PN	Get BMP, Mg next AM
3.0 – 3.4	40 mEq X 2; increase in IV's/PN	Get BMP, Mg next AM; may wish to get stat K 2 hours after second 40 mEq bolus especially if losses are suspected to be high. Reassess.
2.0 – 2.9	40 mEq X 3+; increase in IV's/PN	Get stat K 2 hours after second 40 mEq bolus and reassess; may need 1-2 additional boluses; repeat. Check serum Mg. Reassess.

Table 2. Study subject demographics group one (n=41), patients receiving 40 mEq potassium dose

Subject Demographics	Subject Demographic Data	Mean	Std deviation
Male	36		
Female	5		
Age (years)	18-59	38.7	13.5
Race: Caucasian African American Other/Hispanic	 26 14 1		
Weight	56-100 kg	76 kg	15
BMI	19-33kg/m²	38.7	3.5
40 mEq K dose	n=41		
Dose K		43.341	1.543
Pre-K		3.660	0.216
Post K		3.737	0.360
Difference		0.071	0.374

Table 3. Group 2 patients receiving 60 mEq KCL dose (n=8)

Demographic data and results.

Subject Demographics	Subject Demographic Data	Mean	Std deviation
Male	5		
Female	3		
Age (years)	25-29	42.1	11.5
Race: Caucasian African American Other	 6 1 1		
Weight	45-100 kg	79kg	18
BMI	23-33kg/m²	25.9	3.8
60 mEq K dose	N=8	Mean	Std deviation
Pre-K		3.500	0.214
Post K		3.763	0.342
Difference		-0.263	0.393

Table 4. Group 3 patients receiving 80 mEq KCL (n=8)

Demographic Data and results.

Subject Demographics	Subject Demographic Data	Mean	Std Deviation
Male	4		
Female	4		
Age (years)	28-63	45	12.6
Race: Caucasian African American Hispanic/other	 4 3 1		
Weight	41-91kg	63kg	18
BMI	16-28	22.5	4.9
80 mEq dose	N=8	Mean	Std Deviation
Pre K		3.337	0.130
Post K		3.900	0.602
Difference		-0.563	0.655

APPENDIX B

THE UNIVERSITY OF MEMPHIS

Institutional Review Board approval letter

THE UNIVERSITY OF MEMPHIS

Institutional Review Board

To:	Leeanne Chittom Human Sciences
From:	Chair, Institutional Review Board For the Protection of Human Subjects irb@memphis.edu
Subject:	Evaluation of an intravenous potassium dosing algorithm (062111-795)
Approval Date:	August 10, 2011

This is to notify you of the board approval of the above referenced protocol. This prc was reviewed in accordance with all applicable statuses and regulations as well as et principles.

Approval of this project is given with the following obligations:

1. At the end of one year from the approval date, an approved renewal must be i effect to continue the project. If approval is not obtained, the human consent no longer valid and accrual of new subjects must stop.
2. When the project is finished or terminated, the attached form must be comple and sent to the board.
3. No change may be made in the approved protocol without board approval, ex where necessary to eliminate apparent immediate hazards or threats to subje Such changes must be reported promptly to the board to obtain approval.
4. The stamped, approved human subjects consent form must be used. Photoco the form may be made.

This approval expires one year from the date above, and must be renewed prior to th date if the study is ongoing.

Digitally signed by Brian Schilling
DN: cn=Brian Schilling, o=Univeristy of Memphis, ou=Institutional Review Board Chair, email=bschling@memphis.edu, c=US
Date: 2011.08.10 17:08:01 -05'00'

Chair, Institutional Review Board

THE UNIVERSITY OF TENNESSEE

Institutional Review Board letter of approval

THE UNIVERSITY OF TENNESSEE
Health Science Center

Institutional Review Board
910 Madison Avenue, Suite 60(
Memphis, TN 3816
Tel: (901) 448-482

13 April 2010

LEEANNE CHITTOM
The Med - Regional Medical Center at Memphis

Re: 10-00817-XM
Study Title: Evaluation of an intravenous potassium dosing algorithm.

Dear Dr. CHITTOM:

The Administrative Section of the UTHSC Institutional Review Board (IRB) reviewed your application for the above referenced project.

The Administrative Section of the IRB determined your application to be consistent with the guidelines for **exempt** review under 45 CFR 46.101(b)(4) in that it involves the study of existing data or other materials that are publicly available or the information will be recorded in a way that subjects cannot be individually identified. In accord with 45 CFR 46.116(d), informed consent is waived.

Therefore your application has been determined to comply with proper consideration for the rights and welfare of human subjects and the regulatory requirements for the protection of human subjects. This letter constitutes full approval of your application for the above referenced study.

This study may not be initiated until you receive approval from the institution(s) where the research is being conducted.

In addition, the request for waiver of HIPAA authorization for the conduct of the study itself is approved. The waiver applies to the medical records of patients at the Med treated for hypokalemia between 2-28-08 and 2-28-10.

In the event that volunteers are to be recruited using solicitation materials, such as brochures, posters, web-based advertisements, etc., these materials must receive prior approval of the IRB.

Any alterations (revisions) in the protocol must be promptly submitted to and approved by the UTHSC Institutional Review Board prior to implementation of these revisions. You have individual responsibility for reporting to the Board in the event of unanticipated or serious adverse events and subject deaths.

Sincerely,

Holly Herron

Signature applied by Holly A Herron on 04/14/2010 12:01:54 PM CDT

Terrence D. Ackerman

Signature applied by Terrence F Ackerman on 04/14/2010 12:03:53 PM CDT

Holly Herron
Administrative Research Assistant
UTHSC IRB

Terrence F. Ackerman, Ph.D.
Chairman
UTHSC IRB

THE REGIONAL MEDICAL CENTER AT MEMPHIS

Letter of study approval

Regional Medical Center at Memphis

May 14, 2010

Ms. Leeanne Chittom, BS, RD
Food & Nutrition Services
The Regional Medical Center
877 Jefferson Avenue
Memphis, TN 38103

Dear Ms. Chittom:

The project proposal entitled "*Evaluation of an intravenous potassium dosing algorithm*" **(IRB # 10-00817-XM)** has been reviewed by this office. The goals of the project appear to be consistent with the commitment of the Regional Medical Center to the advancement of medical science and healthcare.

It is my understanding that the MED will not be providing any chargeable services for this study.

For your convenience, the following list will serve as a reminder of some of your responsibilities as the principal investigator at this site. All members of your team must be aware of these requirements to ensure compliance with the MED's policies for conducting research (items applicable to this study have been listed). Please refer to the MED's "Research Policies and Procedures" for a complete listing. If you have any questions, please call the Office of Medical Research at 545-7453.

1. Any **revisions** in the protocol or consent form must be forwarded to the Office of Medical Research.
2. Upon completion of the study, the Research Office must be informed of the end date. A copy of **IRB Form 7** (Report of Termination of IRB Project) can be submitted to meet this requirement.

I commend you for your research activity and look forward to hearing from you regarding the outcome of this study. If our office may be of help to you in connection with this project or with future endeavors, please let us know.

Sincerely,

Jack D. McCue, M.D.
Chief Medical Officer

CC Maria van Werkhooven, Director
Office of Medical Research

877 Jefferson Avenue Memphis, TN 38103 901.545.7100