Author Query:
1. Please provide Conclusion on page 3

Chapter

127

Hyperkalemia: Updates on Outcomes and Therapeutic Strategies

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Introduction

Normal homeostasis of potassium (K), the most abundant cation in the body is crucial in maintaining health. The balance of between intra- and extracellular K is really very important in normal cell membrane electrophysiology in cardiac muscle, skeletal muscle, smooth muscle, and nerve cells[1] Of these, cardiac electrophysiological perturbations are most dangerous leading to arrhythmias, conduction system abnormalities, and asystole. Evidence suggests that both high and low K levels are associated with higher mortality depicting a typical U-shaped association.[2]

Definition of Hyperkalemia

There is no universally agreed or accepted definition of hyperkalemia and may be defined as potassium concentration above the upper limits of normal which is usually >5.0–5.5 mmol/L. Most of the guidelines classify hyperkalemia by severity as mild (5.5–5.9 mmol/L), moderate (6.0–6.4 mmol/L), and severe (>6.5 mmol/L) to help in making clinical decision and formulating therapeutic strategies. Although in practice, treatment strategies depend on the patient's clinical condition and rate of change in the serum K concentration rather than absolute K concentration.[3,4]

Outcome of Hyperkalemia

Hyperkalemia is responsible for increased morbidity and mortality associated with poor outcomes in general population, in population with cardiovascular (CV) and kidney disease and also in critically ill patients.[5] Hyperkalemia, the most common electrolyte abnormalities, is suggested to be unpredictable because arrhythmias, cardiac arrest, and sudden death can occur at any time and is generally fatal at >10 mmol/L of K concentration, but patients with extreme hyperkalemia has been reported to survive. In-hospital patients with hyperkalemia have recorded significantly higher mortality of 18.1% than with hypokalemia (5.0%) or normokalemia (3.9%). Patients of ischemic heart disease (IHD), chronic kidney disease (CKD) or on chronic hemodialysis (HD) have recorded a U-shaped association between potassium levels and mortality.[6]

Severe hyperkalemia patients are reported to be at higher risk and studies reported 30.7% in-hospital mortality, 3–5% of deaths in HD patients, and increase the odds of mortality within 1 day of the event in CKD patients.[6] Evidence showed that prolonged hyperkalemia and acute renal injury (AKI) are independent predictors of in-hospital mortality. Data indicated association of higher mortality and potassium levels of >4.5 mmol/L in patients of acute myocardial infarction (AMI) and heart failure (HF).[5] Clinical presentation of hyperkalemia may include progressive weakness resulting in flaccid paralysis, depressed deep tendon reflexes, and paresthesias. These presentations are benign and ultimately progress to dangerous cardiac rhythm and conduction disturbances. Classic ECG presentation includes peaked T-waves, prolongation of PR interval, loss of P-waves, widening of QRS, bradycardia, and ultimately a sine wave rhythm.[5]

Retrospective data suggested that hyperkalemia manifesting with abnormal ECG had a higher mortality rate. Poor correlation of ECG changes and K levels is also shown by the fact that chronically dialyzed patients

may not show any ECG manifestations of hyperkalemia despite having high K levels.[5] Many observational studies have examined the effect of hyperkalemia on long-term all-cause mortality and suggest more immediate or early adverse effects rather than long-term effects. Supporting this hypothesis, a study conducted in patients undergoing peritoneal dialysis showed an association of hyperkalemia with increased 1-year mortality and no association with long-term mortality. A study conducted in hospitalized patients suffering from AMI showed that K levels of >5.0 mmol/L was associated with higher risk of ventricular fibrillation. A large study involving 245,808 hospitalized US veterans showed association of K levels of >5.5 mmol/L with significantly increased 1-day mortality. It also showed substantially increased risk in subjects having normal renal function as compared to subjects with severe CKD at comparable levels of hyperkalemia. The explanation for less risk in more advanced CKD is unclear, but it can be due to activation of adaptive mechanisms to sustained hyperkalemia in CKD patients.[2]

Evaluation[4]

The ECG is the first and most important investigation in a patient with hyperkalemia, since ECG manifestations provide risk stratification and guide management strategies. It is very important to note that there is poor correlation between increased K levels and ECG changes. The rate of rise in K levels is more important than absolute K levels because chronic hyperkalemia at higher K level may have relatively normal EGCs and sudden rise in K levels may manifest with significant ECG changes at much lower K levels.

Increased K levels generally cause ECG changes in a dose-dependent manner, but the rate of rise of K levels are also important:

- K = 5.5 to 6.5 mmol/L: Tall, peaked T-waves
- K = 6.5 to 7.5 mmol/L: Loss of P-waves
- K = 7.0 to 8.0 mmol/L: Widening of the QRS complex
- K = 8.0 to 10.0 mmol/L: Cardiac arrhythmias, sine wave pattern and asystole

Other ECG changes may include small or absent P wave, prolonged PR interval, augmented R wave, wide QRS, and peaked T waves.

Additional laboratory investigations should include serum blood urea nitrogen, creatinine, urinalysis (renal function), urine potassium, sodium, urine osmolality (cause of hyperkalemia), serum calcium level, complete blood count, serum glucose, blood gas analysis (suspected acidosis), lactate dehydrogenase (hemolysis), creatinine phosphokinases, urine myoglobin (suspected rhabdomyolysis), uric acid, and phosphorus (tumor lysis syndrome).

Pseudohyperkalemia, a false elevation of K levels because of faulty specimen collection, handling, or other causes, is a very common presentation. So differentiation between pseudo- and true hyperkalemia is important before initiating aggressive treatment.

Therapeutic Strategies[3,4,7]

It suggests that the therapeutic strategies for management of hyperkalemia should be guided by the cardiac manifestations identified on ECG rather than absolute K level. Hyperkalemia presenting with ECG manifestations should be considered a potentially life threatening requiring urgent intervention. Severe hyperkalemia without ECG changes should also be managed aggressively because of limitation of ECG in predicting cardiac toxicity.

Generally, a three stage approach is being followed to treat hyperkalemia:

- **Immediate control of cardiac adverse effects of hyperkalemia:** Intravenous (IV) calcium protects the heart by stabilization of the cardiac membranes, reversing the depolarization blockage, while other measures are initiated to correct hyperkalemia. Recommended dose is 10 mL of 10% calcium gluconate or 3–4 mL calcium chloride given IV in 2–3 minutes with cardiac monitoring. The onset of action is in 1–3 minutes and action remains for 30–60 minutes. If there is no change or reoccurrence observed in ECG, then the dose can be repeated. IV calcium should be given carefully if the patient is taking digoxin. To avoid acute hypercalcemia, 10% calcium gluconate can be given with 100 mL 5% dextrose over 20–30 minutes.
- **Rapid lowering of potassium levels by redistribution of potassium into cells:** Intravenous insulin and inhaled beta-2 agonist help rapid lowering of K levels by shifting K into the cells. The recommended dose is 10 units of regular insulin IV with 50 mL of 50% dextrose (25 g glucose in total), action starts in 10–20 minutes, peaks in 30–60 minutes and remains for 4–6 hours. In case of hypoglycemia, 10% dextrose is given at the rate of 50–75 mL/hour closely monitoring the plasma

glucose. If the patient is having hyperglycemia with plasma glucose of >200–250 mg/dL, 10 units of regular insulin should be given closely monitoring plasma glucose levels.

Inhaled beta-2 agonists (albuterol or salbutamol) are useful agents and have additive effect when used with insulin. These agents should not be used without insulin because about 20% of CKD patients are resistant to beta-2 agonist. The recommended dose is 10–20 mg nebulized albuterol in 4 mL of normal saline in 10 minutes. Action starts in 30 minutes, peaks at 90 minutes and remains for 2–6 hours. Beta-2 agonist should be used with caution because of risk of hyperglycemia and tachycardia.

In routine treatment of hyperkalemia, IV bicarbonate has no role except in patients of concomitant acidosis.

- **Removal of potassium from the body:** This is generally done by using sodium–potassium exchange resin binders, diuretics, and dialysis. Sodium polystyrene sulfonate (SPS) increases fecal excretion of K with usual dose of 15–30 g every 4–6 hours given in suspension with 33% sorbitol to avoid constipation. Though SPS is commonly used, but currently it is not favored due to lack of effectiveness and adverse effects, especially bowel necrosis in elderly patients. The new potassium binders patiromer sorbitex calcium and sodium zirconium cyclosilicate present several potential opportunities for clinical application and research.

Loop or thiazide diuretics enhance potassium excretion and may be useful in nonoliguric, volume repleted or hypervolemic patients with sufficient renal function for a diuretic response.

Hemodialysis is the most effective and reliable measure to reduce K levels and peritoneal dialysis is considerably less effective in reducing the K levels. Effectiveness of hemodialysis in reducing the K levels depends on dialysate, blood flow rates, dialysis duration, type and surface area of the dialyzer, and plasma to dialysate K gradient.

Complications of Treatment

The complications of treatment include hypokalemia, hypocalcemia due to bicarbonate infusion, inability to control hyperkalemia, metabolic alkalosis because of bicarbonate therapy, hypoglycemia because of insulin and volume depletion due to dieresis.

Prognosis

Prognosis is excellent in patients presenting with mild transient hyperkalemia if the cause is effectively diagnosed and promptly treated. Acute or sudden onset hyperkalemia, severe hyperkalemia presenting with ECG manifestations or cardiac arrhythmias if not treated rapidly and effectively can be fatal in up to two-thirds of cases. Hyperkalemia is an independent risk factor for death in hospitalized patients.[4]

Conclusion

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