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Acute hyperkalemia in adults

Emine Emektar*

Department of Emergency Medicine, Ankara Atatürk Sanatoryum Training and Research Hospital, Ankara, Turkey
**Corresponding author*

Abstract:

Hyperkalemia is a common, life-threatening medical situation in chronic renal disease patients in the emergency department (ED). Since hyperkalemia does not present with any specific symptom, it is difficult to diagnose clinically. Hyperkalemia causes broad and dramatic medical presentations including cardiac arrhythmia and sudden death. Hyperkalemia is generally determined through serum measurement in the laboratory. Treatment includes precautions to stabilize cardiac membranes, shift potassium from the extracellular to the intracellular, and increase potassium excretion. The present article discusses the management of hyperkalemia in the ED in the light of current evidence.

Keywords:

Acute hyperkalemia, adults, emergency department, hypoglycemia, insulin, potassium

Introduction

Hyperkalemia is a widespread and life-threatening medical condition in chronic renal failure (CRF) patients in the emergency department (ED). Hyperkalemia is detected in 1%–10% of hospitalized patients. Since there is not any specific symptom, it is an electrolyte disorder that is difficult to diagnose clinically. Hyperkalemia causes broad and dramatic presentations including cardiac arrhythmia and sudden death. The treatment includes targeting multiple procedures.

The present article discusses the management of hyperkalemia in the ED in the light of current evidence.

Definition Classification and Clinical Assessment

Potassium (K^+), which is the basic cation of the cell, is important for the stimulation of muscle, nerve, and myocardial cells, in addition to its many functions in the body. Potassium disorders are the leading cause of electrolyte disorders that are commonly encountered in the ED and should be rapidly corrected. Cardiac complications caused by impaired membrane depolarization form the basis of mortality.[1-5] A plasma K^+ level over 5.0 mmol/L is accepted as hyperkalemia.[2] The most common cause is the increase in potassium release from the intracellular area to the extracellular area.[3,4] The specific risk groups include CRF, acute kidney failure, diabetes mellitus, heart failure, severe tissue destruction, nonsteroidal anti-inflammatory drug user, potassium-sparing diuretics, and renin–angiotensin–aldosterone inhibitor groups.[6-10]

Muscle weakness, cardiac transmission abnormalities, or arrhythmias are the most common clinical findings.[11-18] Symptoms are associated with the grade and development rate of hyperkalemia. Hyperkalemia is categorized as mild (5.0–5.5 mmol/L), moderate (5.5–6.0 mmol/L), or severe (>6.0 mmol/L). Although some symptoms

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ORCID:
EE: 0000-0002-6056-4401

Address for correspondence:
Prof. Emine Emektar, Pınarbaşı, Sanatoryum Caddesi Ardahan, Sokak No: 25, 06280 Keçiören, Ankara, Turkey.
E-mail: emineakinci@yahoo.com

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usually appear at concentrations over 6.5 mmol/L, clinical symptoms do not link with plasma potassium in each case. Although the threshold for emergency treatment alters, most of the guidelines suggest immediate treatment if serum potassium ≥6.5 mmol/L with or without electrocardiographic (ECG) findings.[5,18] The most severe adverse effect of hyperkalemia is cardiac toxicity. Findings such as the pointed T-wave, enlargement of the QRS complex, and atrioventricular (AV) delay are detected in the electrocardiography (ECG).[13] Muscle weakness due to hyperkalemia may progress to flaccid paralysis. If respiratory muscles are affected, hypoventilation and respiratory arrest may develop. Hyperkalemia may also cause metabolic, neuromuscular, and gastrointestinal (GI) abnormalities. Neuromuscular effects may include paresthesia, weakness, and/or paralysis.[15,17,19,20] Deep tendon reflexes may or may not be suppressed. However, sensation, diaphragm function, and cranial nerves are typically normal. Most GI effects include diarrhea, nausea, and vomiting. Metabolic disorders contain hyperchloremic metabolic acidemia.[21,22]

When hyperkalemia is detected, the possibility of pseudohyperkalemia (PHK) should be ruled out first. If "real" hyperkalemia is considered, electrocardiography should be performed immediately, and the cardiac effect of hyperkalemia should be revealed.[23]

Laboratory Analysis

Treatment of hyperkalemia needs timely attainment to correct serum potassium measurements. Potassium measure can be performed in the emergency laboratory or at the bedside using a kind of methods. The most frequently used techniques that give results in a short time are blood gas analysis (BGA) and point-of-care testing of whole blood potassium (POC-potassium).[5,24,25] Such measurement methods that may provide fast results may be effective in the triage of life-threatening conditions. Hyperkalemia is randomly determined through laboratory analysis of the electrolytes or through venous or arterial blood gas analyses. However, both blood gas and POC-potassium tests cannot identify hemolysis, which may result in PHK. PHK should be considered in the absence of risk factors for or clinical ECG findings of hyperkalemia.[24] PHK is usually induced by fist clenching pending phlebotomy or excessive tourniquet time, by hemolysis due to mechanical distension in the course of venipuncture, by some hematological diseases such as thrombocytosis and leukocytosis or during transportation.[25-29] Attention should be paid to tourniquet applications in the ED. A significant increase was detected in the serum potassium level between 0.05 mmol/L and 0.5 mmol/L through tourniquet administration in a previous study.[30] Tourniquet duration is critical in triggering hemolysis, and the tourniquet application duration should be kept short to prevent this effect.

The POC-potassium test was shown to provide enough certain results with equated averages among 0.1–0.5 mmol/l when checked with the central measurements.[25,31,32] The use of BGA and POC-potassium tests should be considered in patients who are clinically suspected of hyperkalemia due to symptoms or ECG results and who are at extreme risk (i.e., patients receiving dialysis treatment). Other quick diagnostic tests are useful while clinical decisions are made in the ED. For instance, the blood gas and electrolyte analyses may be defined at the same time in unstable and prearrest patients. Such values obtained from rapid tests are useful for clinical judgment in severe cases of patients with septic shock, severe trauma and rhabdomyolysis, or sudden cardiac collapse.[24] These quick tests would help to define hyperkalemia both in the ED and intensive care unit. The rapidly detected blood potassium level ensures early treatment in the ED. However, for the patients who present with hyperkalemia as the first finding, central laboratory measurements or a point-of-care test in combination with another analysis method should confirm the hyperkalemia case. An ECG is recommended to assess cardiac involvement due to hyperkalemia.

Electrocardiographic Findings in Hyperkalemia

Hyperkalemia affects cardiac functions and causes serious fatal arrhythmias due to the disruption of the membrane depolarization. Myocardial preserving treatment is recommended in patients with cardiac effects and ECG changes. Therefore, ECG findings are crucial for patients with suspected hyperkalemia. The Kidney Disease: Improving Global Outcomes (KDIGO) potassium discussion conference advised the use of a 12-lead ECG and cardiac monitoring for potassium >6.0 mmol/l.[5] It should always be kept in mind that severe hyperkalemia may not necessarily be associated with ECG findings and hyperkalemia may cause to "atypical" ECG findings below specific conditions.[2,5,13,33-35] Therefore, all hyperkalemic patients should be monitored, whether no typical baseline ECG findings are detected. Typical ECG findings caused by hyperkalemia are the prolongation of the PR interval, the T-wave peak, shortening of the QT interval, P-wave flattening, QRS enlargement, and ventricular fibrillation in conventional resources and guidelines.[2,5,13,34] Classical ECG findings due to hyperkalemia may not see in steps. For example, Dodge detected that it can directly advance to ventricular fibrillation from a normal ECG.[35] The ECG in hyperkalemia may be altered by several elements. These elements contain insulin, calcium, serum pH,

and the serum levels of catecholamines, sodium, and osmolality.[36] It should also be noted that the changes in potassium concentration may not cause ECG changes and may be a poor tool for detecting hyperkalemia as it can only show a sensitivity of 34%–43%.[5,13] One of the main factors affecting the ECG findings in hyperkalemia is the rate of increase in potassium. Therefore, ECG findings are more widespread when the potassium level increases quickly, and ECG changes may not be detected in slow changes in potassium.[26,37] ECG findings associated with hyperkalemia also include sinus bradycardia, left bundle branch blocks (BBBs) or right BBBs, and second- or third-degree AV blocks.[5,33] It was demonstrated that QRS prolongation and bradycardia (<50 beats/min) as well as junctional rhythm observed on an ECG are connected with contrary effects. Another condition that may be confused with bradycardia caused by isolated hyperkalemia is the BRASH syndrome. BRASH is a syndrome in which the synergistic effects of AV nodal blockers and renal failure cause severe bradycardia and hyperkalemia. BRASH is an abbreviation for Bradycardia, Renal insufficiency, AV nodal blockade, Shock, and Hyperkalemia.[38] This syndrome is a clinical picture that is encountered in the daily practice of emergency medicine physicians. However, patients are usually treated without identifying this syndrome. The clinical presentation of the BRASH syndrome occurs from the vicious circle between the drugs used by the patients, hyperkalemia, and renal failure.[38,39] Drugs should be investigated carefully, especially in elder patients with chronic renal diseases during daily practice. An ECG is essential in identifying this syndrome from other reasons of bradycardia, for example, isolated hyperkalemia. However, since it does not ordinarily indicate the conventional ECG findings seen with hyperkalemia, it is not sufficient. Typical ECG changes mentioned above are not common in patients with this syndrome.[38-40]

Hyperkalemia Treatment

Urgent treatment includes three main strategies:

1. To ensure membrane stabilization and to antagonize cardiac effects (calcium)
2. To shift the potassium into the cell (dextrose and insulin, sodium bicarbonate, or β2-agonists)
3. To ensure K excretion from the body (via diuretics, oral resins, or dialysis).

Various recommendations have been made in different protocols, and there may be differences between clinical presentations in terms of both treatment preferences and complication rates.

Membrane Stabilization

Intravenous (IV) calcium (Ca^{+2}) salts should be administered directly in patients presenting with ECG findings that may be associated with hyperkalemia.[41,42] IV Ca^{+2} protects the heart against arrhythmias by antagonizing the excitability of the pericardium. It is effective within 3 min with visible improvements of ECG findings (i.e., narrowing of the QRS complex) during that time. The dose should be administered again if it is not effective within 5–10 min. The length of action is shorter, namely 0.5–1 h; therefore, uncontrolled hyperkalemia cases may require repeated doses. Since IV Ca^{+2} does not reduce potassium levels, different interventions are needed immediately.[41-43] There are three conflicts about this subject:

1. Should it be implemented in patients with normal ECG results?
2. Which Ca^{+2} salt should be used?
3. Should calcium be administered in the toxicity of Digoxin?

There is currently no agreement on the usage of IV Ca^{+2} salts in hyperkalemic patients with normal ECG results. Several researchers argued that IV calcium should not be administered in the lack of ECG findings independent of potassium.[44] The logic behind this argument is that an ECG may be a preferable marker of urgent hazard than the serum potassium level itself. Other studies emphasized the insensitivity of ECG in identifying the severity of hyperkalemia.[5,45] This problem increases more with the variability in ECG interpretation. Since the ECG is considered to be the best tool for evaluating heart toxicity, the impact of IV-administered Ca^{+2} is determined by an improvement in the ECG results. However, IV Ca^{+2} salt is not totally risk-free. IV Ca^{+2} treatment should be provided to patients with hyperkalemia-induced changes in their ECG results.[2,41] In addition, KDIGO recommends the administration of Ca^{+2} to all patients with a K^+ >6.5 mmol/l if the potassium level is known, but an ECG or monitoring is not immediately possible, and this recommendation seems quite reasonable for emergency practice.[5]

Which Ca^{+2} salt should be used?

Some experts prefer the use of calcium gluconate over calcium chloride due to decreased tissue toxicity, while some authorities prefer Ca^{+2} chloride because of its theoretically higher bioavailability.[43] It is important to know that the Ca^{+2} amount in Ca^{+2} chloride is approximately three times higher than Ca^{+2} gluconate (2.3 mmol Ca^{+2} for 10 ml/10% Ca^{+2} gluconate and 6.8 mmol Ca^{+2} for 10 ml 10% calcium chloride). Therefore, the use of 30 ml of 10% Ca^{+2} gluconate rather than 10 ml of 10% Ca^{+2} chloride should be given for the administration of the same Ca^{+2} dose. The European Resuscitation Council advises the use of 10 ml of 10% Ca^{+2} chloride for 2–5 min in hyperkalemia patients with ECG findings.[42] In summary, IV Ca^{+2} is advised for both the prophylaxis and treatment of arrhythmias

in hyperkalemia patients. Administration of Ca^{+2} allows time for distinct interventions to be effective in decreasing potassium levels. Both drugs may be safely administered if an IV line is sufficient. The use of 10% Ca^{+2} gluconate requires consecutive doses of 10 ml, whereas a single dose of Ca^{+2} chloride is more likely to be effective. For this reason, an equal Ca^{+2} chloride or gluconate (6.8 mmol) dose is suggested for the first therapy.

Should calcium be administered in the toxicity of digoxin?

Caution with IV Ca^{+2} administration has historically been recommended in patients with suspected or known digoxin toxicity. Since hypercalcemia would worsen the toxicity of digoxin, a slower rate of administration of approximately 30 min was suggested in patients with digoxin toxicity.[46,47] Five cases resulted in death were reported thus far.[48,49] The evidence for cause-effect association is lacking in these case reports. On the other hand, there are literature reports indicating that there are no adverse effects in patients for whom IV Ca^{+2} is administered in the asset of unknown digoxin toxicity.[46,47,50] Novel information obtained from recent studies has shown that there are no worsening results. Levine *et al*. showed that 159 patients with digoxin toxicity, 23 of whom received calcium, did not develop life-threatening arrhythmias within 60 min after Ca^{+2} administration, and the mortality rate was the same between those who were given Ca^{+2} and those who were not.[50] Recent evidence suggests that IV calcium administration seems to be feasible in patients with known or suspected digoxin toxicity.

Potassium Shift to the Intracellular Compartment

Dextrose plus insulin, sodium bicarbonate, or β2-agonists are used for the potassium shift into the cell.

The combination of dextrose and insulin

The combination of dextrose and insulin is the most efficient, mostly preferred, and most reliable combination among these agents. Rapid-acting IV insulin is the most frequently used agent to redeliver potassium via the stimulation of the sodium–potassium ATPase pump. It is usually dosed at 10 units, and it is administered via a quick IV push. Insulin reduces potassium levels by 0.6 mmol/L to 1.2 mmol/L after 1 h, with a beginning of effect <15 min (generally 5–10 min) and a time of furthest effect of 25–30 min.[2,5,51] Dextrose is administered simultaneously to prevent hypoglycemia.[2,11,18] However, one of the most important complications of this treatment is hypoglycemia, and this complication is known to be related to both increased mortality and duration of hospital stays. The prevalence ranges between 8.7% and 75% in retrospective studies.[51,52] Impaired kidney function, absence of diabetes history, lower glucose levels before treatment, lower body weight, and female gender have also been defined as risk factors for the progress of hypoglycemia.[1,51,53] Although hypoglycemia may be prevented by glucose solutions administered with insulin, there are still various interventions on ideal insulin/glucose ratios, doses, and administration times.[51,53] Various recommendations are encountered in different protocols, and there may be differences between clinical presentations in terms of both treatment preferences and complication rates.

A comparison of lower and higher dose dextrose

One of the recent studies on the comparison of lower and higher dose dextrose was the study of Farina and Anderson in which they compared the effects of 25 g of IV dextrose and 50 g of IV dextrose in addition to 10 units of IV insulin on the rates of hypoglycemia development.[51] The patients were matched according to the presence of acute renal failure, CRF, and diabetes in this study, and they were evaluated for hypoglycemia and hyperglycemia after 4 h following insulin administration. There was no statistically significant difference detected for the appearance of hypoglycemia after 60 min following the administration of 10 units of IV insulin in addition to 50 g of IV dextrose when compared to 25 g. While 50 g dextrose administration caused hyperglycemia more in patients at 60 min when compared to the administered 25 g of dextrose, this finding was not prolonged and hyperglycemia rates did not differ between patient groups after 240 min. Furthermore, certain patient populations, such as patients without diabetes or those with pretreatment blood glucose levels below 110 mg/dl, achieved a greater benefit from the use of 50 g of IV dextrose. In addition, the patients had not developed long-term hyperglycemia after dextrose administration at higher doses. In the light of these results, empirical administration of 50 g of dextrose seems to be preferable in hyperkalemia patients with risk factors for hypoglycemia.

Lower and higher dose insulin

Another strategy to reduce the development of hypoglycemia is the administration of lower doses of insulin. Pierce *et al*. did not find a protective effect on the development of hypoglycemia in patients when 5 units of insulin instead of 10 units were administered in addition to 25 g of dextrose.[54] On the other hand, Wheeler demonstrated a statistically significant decrease in the development of hypoglycemia when an insulin dosing protocol according to body weight (0.1 U/kg of body weight up to a maximum of 10 U) was used instead of the standard 10 units in addition to 50 g of dextrose.[53]

According to these results, it does not seem to be recommended to use insulin according to body weight or low dose in order to reduce the risk of developing hypoglycemia.

B-adrenergic agonists

Administration of β-adrenergic agonists has been suggested as an alternative or adjunct to insulin and glucose.[2,5,14,42] Nebulized albuterol is used at doses between 10 mg and 20 mg for hyperkalemia. It was shown that nebulized albuterol reduced potassium levels by 0.6 mmol/l within 30 min after a 10-mg inhaled dose, and by 1.0 mmol/l after 1 h following a 20-mg dose administration, and this effect continued for approximately 2 h.

Sodium bicarbonate

Bicarbonate does not cause a significant decrease in potassium when the pH is normal. However, it may be beneficial in a patient with metabolic acidemia.

Potassium Elimination

Potassium-binding agents (PBAs), loop diuretics, and dialysis are the only agents for the excretion of potassium from the body.[55] Loop diuretics are generally given in the treatment of acute hyperkalemia. However, there are currently no studies that analyzed their effectiveness in removing potassium in this setting. Loop diuretics are probably beneficial in hyperkalemia patients with volume overload such as congestive cardiac failure and likely beneficial in other patients after fluid resuscitation.

There are restricted data on the use of PBAs for the treatment of acute hyperkalemia in the ED.[2,5] PBAs such as patiromer and sodium polystyrene sulfonate (SPS) may be potent. However, the argument for efficacy and beginning of effect is different. SPS was noted to cause serious adverse GI effects including bowel necrosis.[56] Although patiromer has a slower onset of action, a recent study with a small series investigated patiromer use in hyperkalemic patients and found that patiromer remarkably reduced potassium levels after approximately 2 h without any difference in side effects.[57] Sodium zirconium cyclosilicate (SZC) is a new potassium binder that is an extra selective potassium agent. A randomized, parallel-group, placebo-controlled, double-blind, phase II study of SZC investigated the efficacy of insulin plus glucose and SZC as a treatment for hyperkalemia in the ED.[58] Although the authors of this study emphasized that SZC was well tolerated and could be beneficial despite the presence of a similar potassium decrease after 4 h in the placebo and SZC groups, there is not yet enough research on the use of new PBAs in the ED.

Dialysis removes potassium from the extracellular space in the blood in hyperkalemic patients. Dialysis can be considered for patients who have refractory hyperkalemia after treatment or have hyperkalemia with acute renal failure.

Potassium levels are measured frequently in acute hyperkalemia. Since the beginning of effect of insulin plus dextrose and β-adrenergic drugs, which are the potassium-sparing agents, is between 0.5 and 1 h, potassium may be remeasured after 1 h following treatment. Since these drugs do not actually reduce potassium but rather shift the potassium into the cell, hyperkalemia is expected to recur; therefore, reevaluation is essential. If potassium is not removed from the body within this period, peak to higher values may occur within 2–3 h. Moreover, blood glucose level should be controlled in patients receiving insulin-glucose because of the risk of hypoglycemia. The frequency of potassium concentration and blood pressure monitoring, and the requirement of continuous cardiac monitoring depends on the severity of hyperpotassemia and manifestations, the probability of rebound, overall clinical status of the patient, and the treatment response.

Conclusion

Acute hyperkalemia is a widespread problem in the ED with potentially fatal consequences. All patients with K^+ >6 mmol/l should have an ECG and their vital signs should be monitored. Patients at risk should be identified quickly and rapid laboratory tests should be performed and confirmed using biochemical tests where PHK should be excluded. Calcium salts should be administered immediately in all patients with hyperkalemia and ECG findings. Furthermore, measures should be taken to shift potassium into the intracellular compartment (i.e., β-adrenergic agonists or insulin–glucose) and for potassium extraction. Hypoglycemia should be monitored after treatment by measuring glucose levels. Serum potassium concentrations should be reevaluated frequently to monitor the response to treatment and the rebound increase in serum potassium.

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Conflicts of interest

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