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Review Article

Evidence-based perioperative management of patients with high serum potassium level in resource-limited areas: A systematic review

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A B S T R A C T

This systematic review was conducted according to the Preferred Reporting Items for Systematic review and meta-analysis (PRISMA) protocol. Search engines like PubMed through HINARI, Cochrane database, GoogleScholar and ScienceDirect were used to find high-level evidence that helps to draw appropriate conclusions. Potassium is a critical electrolyte for cellular functions and its serum concentration must be precisely maintained between 3.5 and 5.5 mEq/L.

A multidisciplinary approach is crucial to identify and optimise high risk surgical patients prone to hyperkalemia during preoperative assessment. Elective surgery should be deferred in patients with serum potassium level >6 mEq/L during and appropriate management should be initiated.

Given the variable presentation of hyperkalemia, clinicians should have high index of suspicion of potassium disorders among patients with chronic kidney disease, poorly controlled diabetes mellitus, burns, recent major trauma and blood transfusion. In high risk surgical patients with a normal range of serum potassium level drugs like suxamethonium and Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided. Goal direct fluid regimes with 0.9% normal saline, a high threshold for blood transfusion and tight glycemic controlled are recommended. IV calcium gluconate, insulin -dextrose regime and diuretics are the main therapeutic options in patients with severe hyperkalemia.

1. Background

Potassium is a critical electrolyte for normal functioning of a cell and its serum concentration must be precisely maintained between 3.5 and 5.5 mEq/L (1). Multiple physiological mechanisms work together with a view to maintain potassium (K^+) homeostasis, of those the kidney, gastrointestinal organs, several hormones and cellular transport mechanisms are pivotal for potassium regulation. Therefore, disturbance in one or more of these mechanisms may lead to dyskalemia (2).

The resting cell membrane potential is normally dependent on the ratio of intracellular to extracellular potassium concentrations. Intracellular potassium concentration is estimated to be 140 milli equivalent per liter (mEq/L), whereas extracellular potassium concentration is normally about 3.5–5.5 mEq/L. Under some conditions a redistribution of K^+ between the extracellular fluid (ECF) and intracellular fluid (ICF) compartments can result in marked changes in extracellular K^+ without a change in total body potassium content. The loss of 1% or 35 mmol/l of total potassium body content would seriously disturb the delicate balance between intracellular and extra cellular potassium and would result significant physiologic change [1,3,4].

Potassium disorders are common. Studies have shown that hyperkalemia is found in up to 10% among hospitalized patients. Underlying comorbidities, ongoing illness, and some medications are factors that can affect the potassium homeostasis. Therefore, it is important during preoperative assessment to identify the susceptible patients and factors that can possibly affect the body potassium homeostasis during perioperative period and to measure serum potassium level, followed by a step-wise approach towards management and optimization of hyperkalemic patients may help in decreasing morbidity and mortality related to hyperkalemia [2,5,6]. Even though there is no universal definition for hyperkalemia, most of the literatures agree that a serum K^+ level of >5.5 mEq/L is to be considered as hyperkalemia. Hyperkalemia has again been classified as mild, moderate and severe [7–10] (Table 1).

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Table 1
Classification of hyperkalemia.

	Mild (mEq/L)	Moderate (mEq/L)	Severe (mEq/L)
Hyperkalemia (K^+)	5.5–6.0	6.1–6.5	>6.5

1.1. Etiologies of hyperkalemia

Excessive potassium intake, shifts of potassium from intracellular to extracellular compartment and impaired renal potassium excretion is the most common causes of hyperkalemia [11] (Table 2).

1.2. Clinical manifestation of hyperkalemia

The clinical manifestation of hyperkalemia is not specific and may, at times, be over-shadowed by the primary illness of the patient. Therefore, many individuals remain asymptomatic to hyperkalemia. However, in symptomatic hyperkalemia, the symptoms are primarily associated with cardiac and muscular function. Muscle weakness progressing to flaccid paralysis, respiratory difficulties, depressed deep tendon reflexes, paraesthesia and palpitation are the most common manifestations in the patients with symptomatic hyperkalemia [10,12]. Vital signs usually remain normal except occasional bradycardia due to heart block or tachypnea due to respiratory muscle weakness [5]. Although, these manifestations usually occur in severe hyperkalemia, asymptomatic patients with high degree of suspicion of potassium imbalance should be investigated to determine serum potassium level and ECG may be required for immediate medical management [1].

➢ Investigation modalities

These help the clinician to assess the severity of hyperkalemia and to manage its sequelae [13].

- Complete blood count (CBC)
- Urine analysis (U/A): Urine potassium, sodium and osmolality-renal insufficiency
- Blood urea nitrogen (BUN) and Creatinine: suggest renal insufficiency and determine estimated glomerular filtration Rate (eGFR).
- Bloodglucoselevel (BGL): in patient with known or suspected Diabetes mellitus.
- **Electrocardiography (ECG):** The abnormalities in the ECG demonstrate a sequential progression roughly correlating with serum potassium concentration as follows:
  - ➢ Serum potassium level of 5.5–6.5 mEq/L may demonstrate tall peaked T wave or shortened QT interval and ST segment depression
  - ➢ As the serum potassium level increases further, the PR interval becomes prolonged and P wave flattens and eventually lost and this is followed by prolongation of QRS complex.
  - ➢ Ventricular fibrillation may occur when serum potassium level rises to 7.0–8.0 mEq/L. Many of these features may occur simultaneously in case of severe hyperkalemia [14,15].

2. Justification

Many patients with co-morbidities like diabetes mellitus, chronic kidney disease, septicemia, and heart failure are prone to develop hyperkalemia and such patients may undergo elective and emergency surgery [16]. Nowadays, many elderly surgical patients are commonly taking medications like angiotension converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and aldosterone antagonists and these medications can further increase the risk of developing perioperative hyperkalemia and its associated complications [17,18]. Apart from patient factor, Surgery and anesthesia factors like intraoperative tissue damage, extensive tissue dissection during surgery, blood transfusion and suxamethonium may cause intraoperative hyperkalemia in high risk patients [19,20].

Therefore, implementation of evidence based care related to surgical patients with high risk to hyperkalemia may minimize the morbidity and mortality, prevent unnecessary cancellation, decrease prolonged hospitalization and helps to minimize the health care costs.

3. Methods

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guideline [21]. A computerized systematic search of the PubMed, GoogleScholar and ScienceDirect databases were used to find articles. Prospective observational studies, randomized control trials, systematic reviews and audit studies were included in this review using the following Mesh terms: (Hyperkalemia **OR** Potassium **OR** Perioperative hyperkalemia) **AND** (Prevention **OR** treatment) AND (Arrythmia AND insulin AND

Table 2
Causes of high serum potassium.

1. Excessive potassium intake		In patients with end stage renal failure
2. Intracellular shift	Potassium release due to cell lysis	Acute intravascular haemolysis due to infection. Transfusion reaction. Tumor lysis syndrome (chemotherapy). Severe haemolytic anemia Extensive burns Rhabdomyolysis Ischemic colonic necrosis.
	Potassium release with intact cell membrane	Drugs inhibit Na^+-K^+ ATPase (Beta adrenergic receptor blockers promote K^+ shift out of cells which is usually less than 0.5mEq/L). Succinylcholine (In healthy individuals, K^+ rise is less than 0.5meq/L but it is much higher in patients with kidney failure, neuromuscular disease, extended burns or tetanus).
	Metabolic acidosis	K^+ will shift from ICF to ECF in exchange of H^+
3. DKA or severe hyperglycemia with out ketoacidosis	Insulin deficiency	Massive eeflux of potassium to plasma
4. Impaired renal K^+ excretion		As kindney function worsens and urine out put is reduced, decreased Na^+ and water reabsorption and hyperkalemia ensues.

salbutamol AND calcium AND dialysis AND surgery AND anesthesia (Fig. 1**)**. In this review, publication dates were used as inclusion or exclusion criteria and research papers published since 2000 were included. Only those human studies published in English pertaining to the treatment of hyperkalaemia were considered for this review. After comprehensive and in-depth appraisal of literature, evaluation of quality was conducted by categorizing them into levels: **1a** (Meta-analysis, systematic review of RCTs, Evidence based guidelines), **1b** (Systematic review of one RCT), **1c** (RCTs), **2a** (Systematic review of cohort or case control studies) and 3**a** (Non analytical studies like case report and case series, Clinical audits, commentaries) (Table 3) based Good clinical practice, GCP, WHO, 2011. Finally, conclusion has drawn based the level of evidences.

4. Discussion

4.1. Preoperative assessment

Careful history and physical examinations are paramont components of preoperative assesment for identifying patients who are prone to develop perioperative hyperkalemia [16]. For the purpose of risk stratification, the clinician should address the crucial factors like etiology, clinical manifestation and the effect of the medications used preoperatively, on potassium homeostasis. In addition, evaluation of the laboratory investigation results and ECG is a prerequisite in those patients who are prone to develop intraoperative hyperkalemia [22].

Although there is no clear cut point regarding serum potassium level for the purpose of postponing the surgery or proceeding with the surgery, it has been observed that the patients with a serum potassium level >5.5 mEq/L in their preoperative period are twice as likely to require intraoperative management for hyperkalemia as compared to the patients with a preoperative serum potassium level ≤5.5 mEq/L [23][1a.] Furthermore, symptomatic patients with a preoperative serum potassium level <5.5 mEq/L requires intervention prior to surgery [16][1a.]

Suxamethonium may cause a rise in serum potassium level in the range of 0.5–1.0 mEq/L in normal patients and the rise may exceed even 2 mEq/L in a category of patients who are suffering from burn, massive trauma, neurological lesion and certain myopathies and this rise may sustain for a period of up to 10–15 min time [20,24,25][2a]. Therefore, it is advisable to avoid suxamethonium in the above mentioned category of patients.

Non-steroidal antiinflammatory drugs (NSAIDs) may mimic perioperative hyperkalemia because of their effect on renal arterioles and direct nephropathy. Therefore, it stands advisable to avoid NSAIDs in high risk patients [26][2a] (Table 4).

Regarding laboratory measurement of serum potassium, the clinician needs to be careful as pseudohyperkalemia is one of the important differential diagnosis for hyperkalemia [13][3a]. This

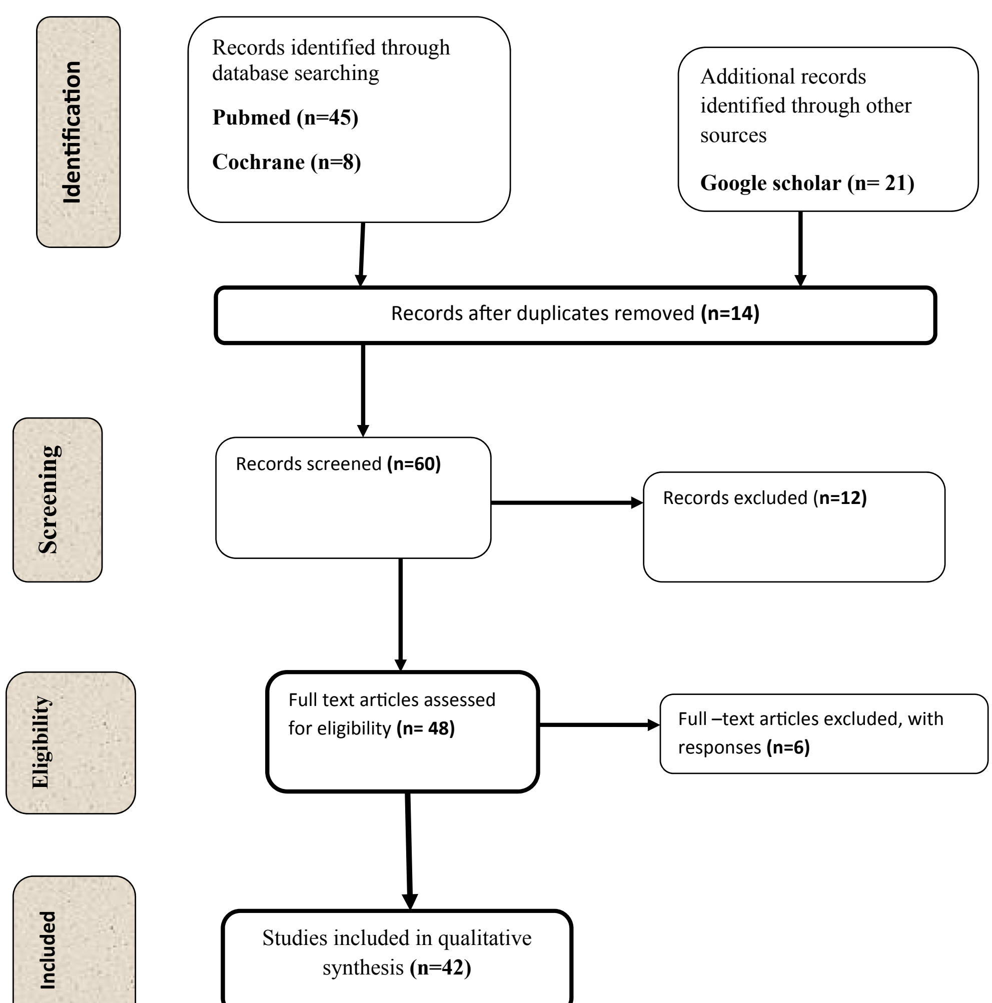

Fig. 1. Flowchart for selection of studies by PRISMA flow diagram.

Table 3
Levels of evidence and degree of recommendations.

Level	Types of evidence	Degree of recommendation
1a	Meta analysis, systematic review of RCTs, Evidence based guidelines	Strongly recommended and directly applicable
1b	Systematic review of one RCTs	Highly recommendable and directly applicable
1c	Randomized control/clinical trials	Recommended and applicable
2a	Systematic review of cohort or case control studies	Extrapolated evidence from other studies
3a	Non analytical studies like case report and case series, clinical audit, commentaries and export opinions	Extrapolated evidence from other studies

Source: Good clinical practice, GCP, WHO, 2011.

Table 4
Strategies to prevent intraoperative and postoperative incidental hyperkalemia in high risk patients.

High risk surgical patient for incidental hyperkalemia	Perioperative consideration to prevent incidental hyperkalemia in high risk patients
➢ Patients with acute kidney injury or chronic kidney disease	• Avoid depolarizing muscle relaxants and use non depolarizing muscle relaxants for induction and maintenance.
➢ Recent history of blood transfusion	• Goal directed fluid management (maintained adequate urine output, use 0.9% normal saline), avoid Hartmann's solution.
➢ Patient with congestive heart failure	• Minimize or avoid blood transfusion
➢ Cirrhosis	• Avoid intraoperative administration of NSAIDs
➢ History of taking medications like ACE inhibitors, angiotensin II receptor inhibitors, NSAIDs and Potassium sparing diuretics.	• Well controlled intraoperative plasma glucose level in diabetic patients
➢ Severe trauma, burns, invasive and major surgery	• Hyperventilation (PaCO2 25–30 mmHg).
➢ Diabetic ketoacidosis, poorly controlled diabetes mellitus	• Use 12 –lead ECG and monitor for ECG changes
	• Meticulous and close observation during post operative period (haemodynamic status, volume status)

occurs due to haemolysis of the blood sample sent to the laboratory and this is induced by poor venipuncture technique, excessive clotting of the blood sample, hereditory spherocytosis or familial hyperkalemia. In hereditory spherocytosis and familial hyperkalemia, lowering of ambient temperature induces the movement of the intracellular potassium out into the extracellular fluid. Pseudohyperkalemia can be diagnosed by demonstrating a lower potassium concentration in plasma than in serum [23] **1b**. Therefore, in order to exclude pseudohyperkalemia, plasma potassium also should be measured from a heparinized sample of whole blood [27] **1b** .

4.2. Management of intraoperative hyperkalemia

Incidence of intraoperative hyperkalemia during living-donor liver transplantation is about10.4% [23] while patients undergoing parathyroidectomy has 55% risk of Intraoperative hyperkalemia [28] **1a**. Furthermore, patients undergoing kidney transplant surgery are more than twice as likely to require intraoperative treatment for hyperkalemia if their preoperative serum potassium was ≥5.6 mEq/L as compared to patients with a preoperative serum potassium of ≤5.5 mEq/L [29] **1a**.

Hyperventilation with (Paco$_2$ 25–30 mmHg) is tend to decrease serum potassium as it clears acidosis [16] **1b**. Blood transfusion has to be minimal [19] and intra operative blood loss should be replace by normal Saline 0.9%. Intraoperative monitoring of serum potassium, ECG change, capillary glucose level and urine output will improve patient outcome [1,16,22] **1c**.

4.3. Postoperative period

After the surgery is over, the patients often become volume depleted, acidotic, require blood transfusion or exposed to factors which may further impair renin-angiotensin-aldosterone system and activation of sympathetic nervous system leading to further increase in serum potassium level. Therefore, the patients should be monitored during the postoperative period for recurrent hyperkalemia [19].

4.4. Pharmacologic interventions of intraoperative hyperkalemia

The management of perioperative hyperkalemia depends upon certain factors like cause & severity of hyperkalaemia and urgency of the management. The therapeutic options for hyperkalemia can conveniently be grouped into the following categories (Table 5).

- Those that minimize the cardiac effects of hyperkalemia
- Those that induce potassium uptake by the cells
- Those that remove potassium from the body

4.4.1. Drugs used to minimize the cardiac effects of hyperkalemia

Intravenous calcium: Administration of intravenous calcium is an urgent management modality which is directed towards the restoration of transmembrane electrical gradient of the cardiac myocytes.This stabilizes the myocardium by reducing the resting membrane potential of the myocytes [30] **1a** . The precise mechanism is poorly understood.

Calcium is available in two formulations: calcium gluconate and calcium chloride. 10 ml of 10% Calcium gluconate is preferred, because of its lower risk of tissue necrosis in case of tissue extravasation, allowing it to be safely administered into a peripheral vein. In contrast, calcium chloride contains a higher concentration of calcium, necessitating its administration via a central line [31] **1a**.

Intravenous calcium starts acting within 5 min, but it has short duration of action. So that, repeated dose and continuous ECG monitoring may necessary in some patients. In patients taking digoxin, repeated doses of calcium are not recommended because of the risk of arrhythmias. Calcium has no role in reduction of serum potassium. For this reason calcium administration should be followed closely by treatments to shift potassium into the cells and remove it from the body [32] **1a.**

Table 5
Summary of therapy options for hyperkalemia.

Medication	Recommended doses, route of administration	Onset
Calcium gluconate	10 ml of 10%,IV	1–3 min
Insulin –glucose regime	10 IU with 50 ml of 50% dextrose via infusion	20 min
Furosemide	40–80 mg based on the haemodynamic status and Urine out put of the patient	15 min

4.4.2. Drugs used to decrease plasma potassium through different mechanisms

Insulin: The adenosine triphosphatase sodium-potassium pump (Na^+-K^+-ATPase) in the cell membrane of skeletal muscle rapidly transports potassium into the cells, and it is stimulated by synergistically by insulin and by β2 adrenergic agonists. Insulin accelerates the intracellular movement of potassium into muscle cells by binding to its receptor on skeletal muscle. Once this occurs, the abundance and activity of sodium-potassium adenosine triphosphatase (Na^+-K^+ATPase) and glucose transporter on the cell membrane increase through independent signaling pathways (32)[1a.]

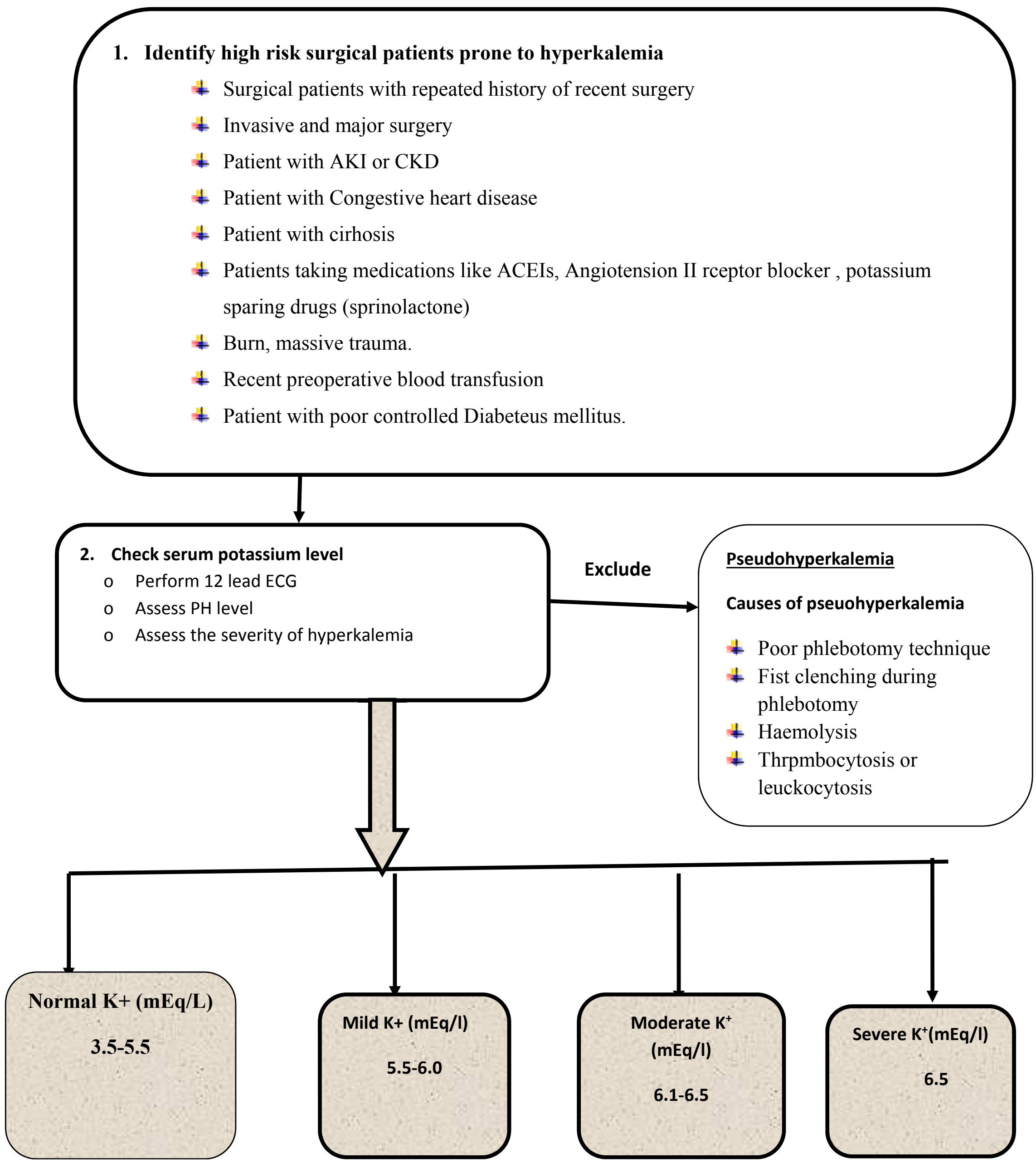

Fig. 2. Flow chart for risk stratification and management of perioperative hyperkalemia.

The most commonly recommended regimen is a bolus injection of short-acting insulin. If the blood glucose is < 250 mg/dL, 25 g of glucose should also be given (50 mL of a 50% solution) to offset hypoglycemia due to insulin administration [33–35][1a].

Cochrane Database of Systematic Review of seven RCT's on Pharmacological interventions for the acute management of hyperkalaemia showed that iv insulin-dextrose and salbutamol are used as first line therapy in the acute management of hyperkalemia is more effective than either therapy alone but triple therapy with insulin-dextrose, salbutamol and bicarbonate was found to be less effective than dual therapy (36)[1a].

β2- Agonists: β2-adrenergic agonists induces intracellular potassium movement by up-regulating the activity of Na^{+}- K^{+} ATPase in skeletal muscle by a cellular pathway distinct from that caused by insulin. Thus, the potassium-lowering effects of insulin and β2-adrenergic agonists are additives in their action [37]. Intravenous β2 - Agonists are not available in most of the developing countries. Nebulized salbutamol 10–20 mg which is equally effective given intravenously is used as adjuvant therapy for moderate or severe hyperkalemia as it promotes the intracellular shift of K+ by activation of the Na–K ATPase pump (37)[1a].

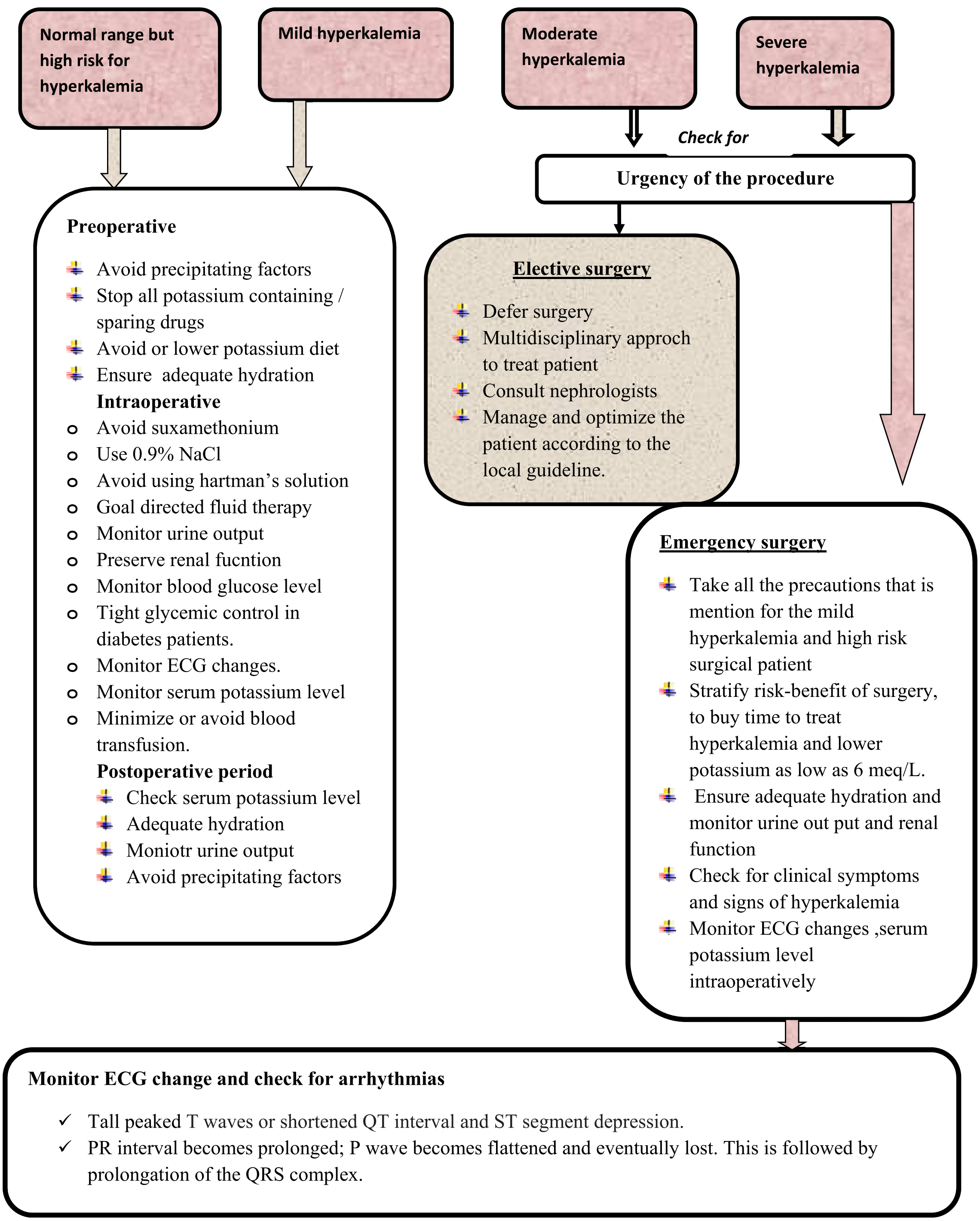

Fig. 2. (*continued*).

Sodium Bicarbonate: Sodium bicarbonate works to shift potassium intracellularly but is not considered first-line management of hyperkalemia due to controversial data regarding efficacy and safety concerns. Boluses of 1 ml/kg of sodium bicarbonate of 8.4% solution have been suggested [38][1b]. Studies have shown that sodium bicarbonate was not able to decrease serum potassium significantly or rapidly, with onset of action potentially taking hours [35]. Its use in patients with metabolic acidosis and hyperkalemia was also reported to be controversial [39]. Sodium bicarbonate can potentially increase fluid load, causing hypernatremia and metabolic alkalosis, and should therefore be used with caution in patients with heart failure and chronic kidney disease (CKD) because of sodium load. If infused rapidly, it can be metabolized to carbon dioxide, or in those with respiratory insufficiency, can result in acidosis or hyperkalemia. IV sodium bicarbonate may be helpful in patients who require fluid loads [35][1a.]

Diuretics: Following the use of methods to shift potassium into cells, strategies should then be undertaken to eliminate excess potassium. In patients with adequate kidney function, loop diuretics combination with thiazide diuretics can be used for the excretion of potassium. Onset of action is 15–60 min. However, it should be noted that although diuretic-induced volume depletion can lead to decreased distal nephron flow and reduced potassium excretion, volume-expanded patients will benefit from diuresis (32)[1a].

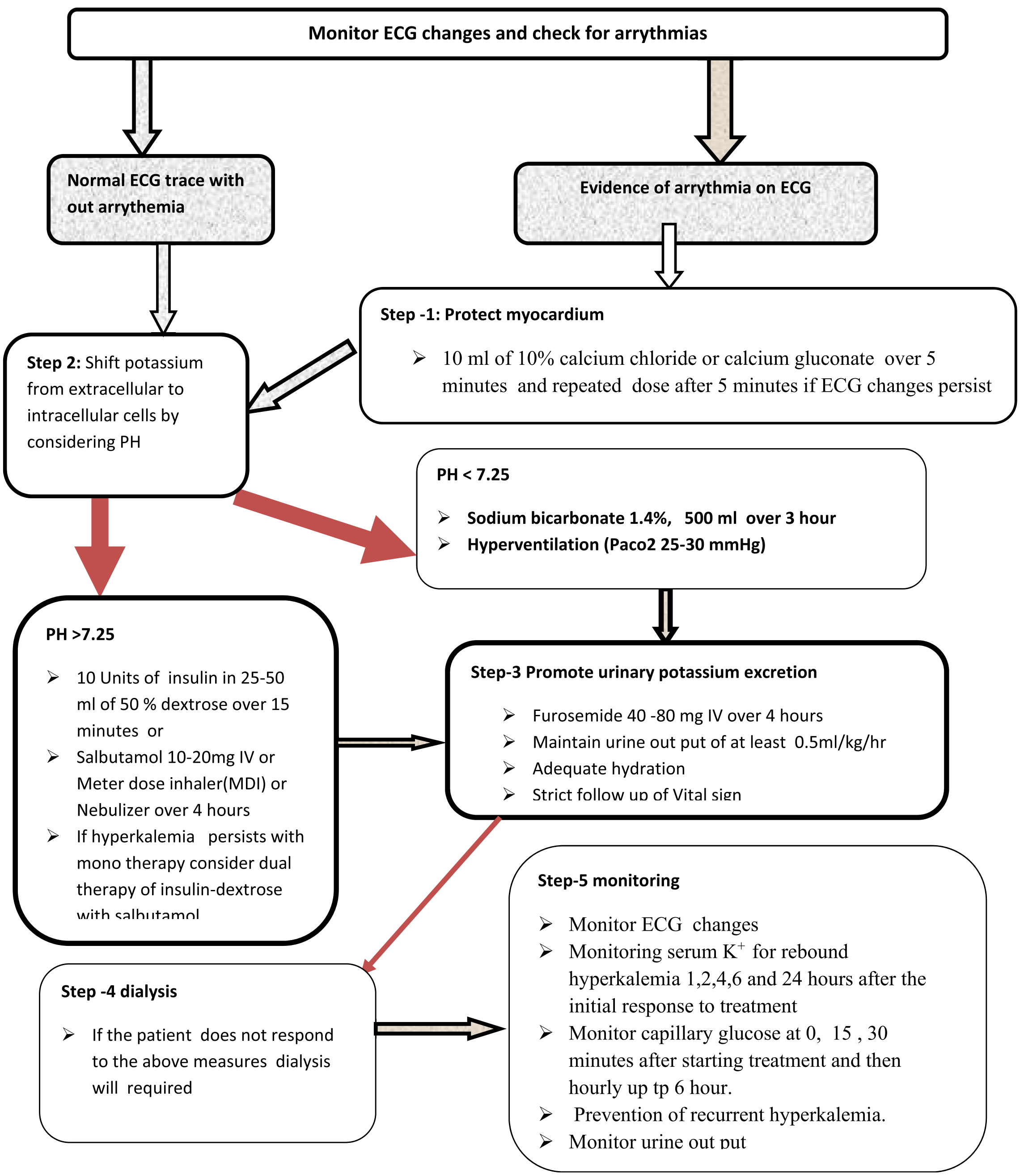

Fig. 2. (*continued*).

4.4.3. Postoperative monitoring

After the initiation of management for hyperkalemia, the patient needs to be monitored as follows:

- Continuous real time ECG to detect any change
- Check serum potassium for rebound hyperkalemia at 1, 2, 4, 6, and 24 h after the initiation of management.
- Check capillary blood glucose immediately after the initiation of management and then after 15 and 30 min and then every hour up to 6 h.

5. Area of controversies

- Systematic review study by Harel&Kamel in 2016 has shown that there is no statistically significant difference between the regimens of 10 IU and 20 IU of soluble insulin in acutely lowering the serum potassium concentration [40]**1a**.
- A study by Alfonzo and his collegues in 2006 has shown the regimen of 20 IU of soluble insulin has a higher profile in reducing serum potassium, but at the same time has higher hypoglycemic effect [22].
- Another two cochrane data base systematic reviews recommend to use 10 IU of insulin [36, 39].
- A randomized control trial done in 2014 has recommended to use IV bolus dose of glucose as it significantly decrease serum potassium [41].
- Two Cochrane database systematic reviews recommend insulin with dextrose as glucose alone is not as effective as insulin or other potassium-shifting therapy [36,42].
- Another study recommends to use insulin-dextrose therapy rather than using glucose alone in nondiabetics because it causes insufficient release of endogenous insulin which further paradoxically increases serum potassium [22].
- A Cochrane database systematic review in 2015 compared intravenous salbutamol with nebulized salbutamol and concluded that salbutamol administered through any route is effective in lowering serum potassium [42]. However, another study by Elliott et al., in 2010 concluded that intravenous salbutamol is less efficacious than nebulized salbutamol [33].

6. Conclusion

Although there is scarcity of data on the incidence of hyperkalemia among patients for major surgery, an elevation of plasma potassium may occur frequently in hospitalized patients. Therefore, it is crucial during preoperative assessment to identify the high risk patients who may develop intraoperative hyperkalemia and to formulate strategies to reduce intraoperative hyperkalemia.

Severe hyperkalemia is a life-threatening condition and its clinical presentation is variable. Therefore, the clinician must maintain a high index of suspicion, specially in patients with chronic renal disease, poorly controlled diabetes mellitus, recent burn, recent major trauma, recent blood transfusion and hospitalized patients. During preoperative assessment of the patients with high risk for developing intraoperative hyperkalemia, serious attention should be paid to plasma potassium concentration and ECG. Furthermore, duration of symptoms and signs and the cause should be identified before elective surgery. There is no clear cut point regarding serum potassium level at which elective surgery is to be postponed. However, patients with preoperative serum potassium level >6 mEq/L should not be recommended for elective surgery.

The clinician should formulate the best possible management strategy in patients who are at high risk of developing incidental intraoperative hyperkalemia. The management strategies to prevent incidental intraoperative hyperkalemia should include tight glycemic control, meticulous ECG monitoring, high threshold for blood transfusion, goal directed fluid therapy preferably with 0.9% NS and avoiding suxamethonium and NSAIDs.

The management of perioperative hyperkalemia depends upon the severity, cause and urgency of the procedure. The treatment options for intraoperative hyperkalemia can conveniently be grouped under three categories, i.e. those that minimize the cardiac effect of hyperkalemia, e.g. intravenous calcium gluconate, those that induce potassium uptake by the cells, e.g. insulin-dextrose regime and those that remove potassium from the body, e.g. diuretic. Intravenous calcium gluconate helps in stabilizing the cell membrane of myocardium and it is recommended if the serum potassium level is > 6.5 mEq/L with or without ECG changes (Fig. 2).

Ethical approval

Ethical approval is not required.

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Author contribution

All authors have participated in the stages of evidence searching, development, presentation and implementation of this evidence-based guideline. Especially all authors critically appraise literatures and present it to peers for discussion. Finally, all authors have been participated in identifying areas of need to produce appropriate recommendations.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Guarantor

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Research registration unique identifying number (UIN)

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijso.2019.10.006.

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