DEVELOPMENT AND EVALUATION OF A GUIDELINE ON POTASSIUM CHLORIDE INTRAVENOUS SUPPLEMENTATION: EFFECTIVENESS, SAFETY AND COST IMPLICATIONS

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LIST OF ABBREVIATIONS

A&E	Accident and Emergency
ECG	Electrocardiogram
ICU	Intensive Care Unit
JEPeM	Jawatan Kuasa Penyelidikan Etika Manusia
KCL	Potassium Chloride
NaCL	Sodium Chloride
NMRR	National Medical Research Register
NMSC	Normah Medical Specialist Centre
USM	Universiti Sains Malaysia

LIST OF APPENDICES

PEMBANGUNAN DAN PENILAIAN GARIS PANDUAN MENGENAI SUPLEMEN INTRAVENA KALIUM KLORIDA: KEBERKESANAN, KESELAMATAN DAN IMPLIKASI KOS

ABSTRAK

Suntikan kalium klorida pekat yang digunakan dalam penambahan kalium secara intravena dalam rawatan hipokalemia mempunyai risiko hiperkalemia dan kesilapan pengubatan. Kajian ini bertujuan untuk menghasilkan garis panduan yang mengutamakan penggunaaan rumusan pracampur dalam penambahan kalium secara intravena dan menilai keselamatan, keberkesanan, dan implikasi kosnya. Fasa I kajian ini melibatkan satu kajian tinjauan dalam kalangan 207 doktor perubatan yang bekerja di hospital-hospital Malaysia. Hasil keputusan tinjauan ini menunjukkan bahawa terdapat variasi dalam amalan doktor-doktor perubatan dalam penambahan kalium secara intravena untuk rawatan hipokalemia. Analisis menujukkan latar belakang doktor perubatan yang berbeza menyebabkan variasi ini yang mungkin disebabkan oleh kekompleksan klinikal dan ubat-ubatan pesakit hipokalemia. Ini merumitkan rawatan hipokalemia dan menyokong keperluan untuk mempunyai garis panduan umum yang boleh digunakan dalam pelbagai keadaan klinikal. Kajian tinjauan ini juga menunjukkan bahawa doktor-doktor perubatan di Malaysia menyokong penggunaan rumusan pracampur kalium klorida di mana ia lebih mudah digunakan dan lebih selamat untuk pesakit. Fasa 2 kajian ini melibatkan pembentukan garis panduan penambahan kalium secara intravena yang mengutamakan penggunaaan rumusan pracampur dan dilaksanakan di sebuah hospital swasta. Keputusan kajian mendapati peratusan pesakit hiperkalemia dalam

kumpulan semasa pelaksanaan garis panduan (n = 28) tidak menunjukkan perbezaan yang signifikan daripada kumpulan sebelum pelaksanaan garis panduan (n = 154) (0.0% lawan 3.2%, p =1.000). Peratusan pesakit hipokalemia yang berjaya dipulihkan paras kalium yang rendah dalam kumpulan semasa pelaksanaan garis panduan (n = 28) juga tidak berbeza secara signifikan dengan kumpulan sebelum pelaksanaan garis panduan (n = 154) (71.4% lawan 59.1%, p = 0.218). Penggunaan rumusan pracampur telah menurunkan kos keseluruhan penambahan kalium secara intravena semasa fasa pelaksanaan garis panduan disebabkan oleh pengurangan kos tenaga kerja. Jumlah kos penambahan kalium untuk kes-kes hipokalemia ringan berkurang dari RM 376.19 semasa sebelum pelaksanaan garis panduan kepada RM 263.19 semasa pelaksanaan garis panduan. Jumlah kos penambahan kalium untuk kes-kes hipokalemia sederhana ke teruk pula berkurang dari RM 304.17 semasa sebelum pelaksanaan garis panduan kepada RM 207.29 semasa pelaksanaan garis panduan. Oleh kerana sasaran sampel saiz dalam kajian ini tidak dicapai, ia mungkin menyumbang kepada perbezaan yang tidak signifikan di antara kumpulan dari segi keselamatan dan keberkesanan. Secara keseluruhanannya, garis panduan yang mengutamakan rumusan pracampur ini adalah selamat dan berkesan serta mampu memberi penjimatan kos untuk institusi ini. Penemuan kajian ini menyokong institusi perubatan lain untuk membentuk dan melaksanakan garis panduan untuk penambahan kalium secara intravena dan mengutamakan penggunaan rumusan pracampur.

DEVELOPMENT AND EVALUATION OF A GUIDELINE ON POTASSIUM CHLORIDE INTRAVENOUS SUPPLEMENTATION: EFFECTIVENESS, SAFETY AND COST IMPLICATIONS

ABSTRACT

The concentrated potassium chloride injection used in intravenous supplementation of potassium in hypokalemia is associated with risks of hyperkalemia and medication error. This study aimed to develop a guideline on potassium chloride intravenous supplementation with the emphasis of using premixed formulations and evaluate its safety, effectiveness and cost implications. In Phase I of this study, a nationwide survey was conducted among 207 Malaysian hospital physicians. The findings suggested that there were variations in Malaysian physician's prescribing practice of intravenous potassium supplementation in the treatment of hypokalemia. Data analysis revealed different physicians background resulted in different prescribing practices which may be due to the complexity of patient's clinical conditions and medications. This poses a challenge for prescribers to treat hypokalemia and supports the need to have a practical or general guideline that can be used under different clinical conditions. This survey also revealed that Malaysian physicians favoured premixed potassium chloride formulations where physicians find it would ease usage and is safer for the patient. In Phase II of this study, a guideline with emphasis of premixed formulations was developed and implemented in a private hospital. The study findings revealed the proportion of patients with hyperkalaemia during guideline implementation phase (n = 28) were not significantly different from pre-guideline implementation phase (n = 154) (0.0%

versus 3.2%, p = 1.000). The proportion of hypokalaemic patients with successful corrected potassium levels during guideline implementation phase (n = 28) were also not significantly different from pre-guideline implementation phase (n = 154) (71.4% versus 59.1%, p = 0.218). The used of premixed formulations in this guideline led to an overall cost reduction compared to concentrated formulations during pre-guideline implementation due to the reduction in labour costs. The total cost of intravenous potassium supplementation in mild hypokalaemia cases was reduced from RM 376.19 during pre-guideline implementation phase to RM 263.19 during guideline implementation phase. Meanwhile, the total cost of intravenous potassium supplementation in moderate to severe hypokalaemia cases was reduced from RM 304.17 during pre-guideline implementation phase to RM 207.29 during guideline implementation phase. As the targeted sample size was not successfully achieved in this study, it may have contributed to the non-significant differences between the two phases in terms of safety and effectiveness. In summary, the developed guideline with the emphasis of premixed formulations is safe and effective with potential of cost savings for this institution. Results of this study supports recommendations for other institutions to develop and implement a guideline on intravenous potassium supplementation and to use premixed formulations whenever possible.

CHAPTER 1

GENERAL INTRODUCTION

1.1 Introduction

Potassium replacement is the basic treatment for hypokalaemia and is usually initiated when blood tests reveal a potassium level of below 3.5 mEq/litre. Potassium chloride, which comes in an intravenous and oral form, is commonly used due to its rapid effectiveness in potassium depletion and is especially preferred in chloride-responsive metabolic alkalosis (Asmar, Mohandas & Wingo, 2012). In Malaysia, slow-release tablets and the concentrated injection of potassium chloride (1 g in 10 mls ampoule) is mainly used for hypokalaemia, though other less common formulations which include oral potassium citrate and potassium phosphate injection do exist (Malaysian National Pharmaceutical Regulatory Agency, 2019b). Potassium phosphate is used in hypokalaemia patients with co-existing phosphate deficiency while potassium citrate is given if the patient is presenting with acidosis (Asmar, Mohandas & Wingo, 2012).

Oral potassium is always preferred compared to the intravenous route for the treatment of hypokalaemia due to its better safety profile (Kardalas et al., 2018). However, the intravenous route is needed in certain situations, such as when rapid correction is needed or when gastric absorption is impaired (Kardalas et al., 2018). Treatment through the intravenous route has been associated with serious and potentially fatal risks. Hyperkalaemia can occur when the rate of potassium administration overwhelms the body's acute regulation of potassium (Asmar, Mohandas & Wingo, 2012). The concentrated formulation of potassium chloride injection also needs to be diluted before administration and unfortunately has been associated with fatal medication errors (Ponce et al., 1985; David, 2000; Rastergar &

Soleimani, 2001; David & Hyland, 2002; Wetherton et al., 2003; Reeve, Allinson & Stevens, 2005). Therefore, medication safety organizations have categorized the concentrated potassium injection (1g in 10 mls), that is used in intravenous potassium supplementation as a high alert drug and has recommended several strategies to reduce the risks associated with its use (Joint Commission, 1999; Institute for Safe Medication Practices, 2017). In Malaysia, it is also listed as one of the twenty classes or categories of high alert drugs by the Malaysian Pharmaceuticals Services Division (Malaysian Ministry of Health, 2011).

One of the strategies in ensuring the safety and efficacy of concentrated potassium chloride injection in the treatment of hypokalaemia is implementing clear guidelines. The guideline should include multiple forcing functions such as maximum concentration, rate of infusion, dosage limits and patient monitoring (David & Hyland, 2002; Tubman *et al.*, 2005; Barras *et al.*, 2014). Several institutions have implemented their own guidelines on potassium intravenous supplementation in the treatment of hypokalaemia which are available via the internet (East Cheshire Trust, 2015; Queensland Health Medicines Regulation and Quality, 2016; Royal Cornwall Hospitals, 2019). In Malaysia, information on potassium replacement in hypokalaemia is mentioned in The Critical Care Handbook by the Malaysian Pharmaceutical Services Division and The Malaysian Clinical Practice Guideline for Diabetes Mellitus (Malaysian Ministry of Health Pharmaceutical Services Division, 2013; Malaysian Ministry of Health, 2015). It is unknown whether the hospitals in Malaysia have their own guidelines on intravenous potassium supplementation for hypokalaemia, though dilution protocols may exist (Hospital Tengku Ampuan Rahimah, 2017).

International medication safety organizations recommend the incorporation of premixed formulations in these guidelines to replace the concentrated form of potassium injection (Shlom & May, 2006; International Medication Safety Network, 2019). Premixed formulations are ready-to-use formulations where it eliminates the need to reconstitute before administration. Besides providing the advantage of efficiency, premixed potassium chloride injections promotes safety by eliminating the risk of bolus administration or wrong dilution (David, 2000; David & Hyland, 2002). It is undeniably that premixed formulation is a technological advancement which is widely used in other countries such as in Australia and the United States of America (Van De Vreede, Wilson & Dooley, 2008; Pedersen, Schneider & Scheckelhoff, 2009). Unfortunately premixed drugs are not widely available in Malaysia and premixed potassium chloride injection was only registered in 2009 (Malaysian National Pharmaceutical Regulatory Agency, 2019b). To the best of our knowledge, currently only two private hospitals are using premixed potassium injections in Malaysia.

1.2 Evidence on the safety and effectiveness of intravenous potassium supplementation guidelines and the use of premixed formulations

Despite the available of recommendations and guidelines on intravenous potassium supplementation, variations exists regarding the dose, concentration, rate, duration, route of potassium chloride injection or how rapid potassium correction should be in hypokalaemia (Singhi, Gautham & Lal, 1994; Harrington, 2005). For example, some recommendations of initial intravenous potassium dosing is stated as 10 – 40 mmols per hour (Foringer, Norris & Finkel, 2011; Viera & Wouk, 2015). Meanwhile, others recommendations are stated by hypokalaemia levels, where initial

doses of 20 – 40 mmols are recommended for mild to moderate hypokalaemia and 40 - 80 mmols for severe hypokalaemia (Kraft *et al.*, 2005). Others merely state the recommended daily doses which ranged between 75 - 100 mmols per day (Kardalas *et al.*, 2018). Variations also exist in recommended maximum rate of infusions which are between 10 - 40 mmols per hour and maximum concentrations between 40 – 200 mmols per litre (Malaysian Ministry of Health Pharmaceutical Services Division, 2013; Vanderbilt University Medical Centre, 2016; Royal Cornwall Hospitals, 2019). The reasons for these variations may be due to the fact that normalizing potassium levels is dependent on many factors (Kardalas *et al.*, 2018). Potassium homeostasis can be affected by the patient's clinical condition, hormones, pH balances and concurrent medications taken by the patient (Kardalas *et al.*, 2018). The variations among different institutions may also reflect that the guidelines are tailored to suit their patient population and prescribing practices.

Evidence of effectiveness of these guidelines in the treatment of hypokalaemia is also lacking. There is no guideline on the treatment of hypokalaemia by any major medical association (Weir & Espaillat, 2015). A search in the Cochrane Database of Systemic Reviews with keywords of 'hypokalaemia', 'potassium disorders' and 'electrolyte disturbances' revealed only one review on hyperkalaemia management (Batterink, Cessford & Taylor, 2015). Besides, only a few of randomized controlled studies on hypokalaemia management are available (Ashurst *et al.*, 2016). Several hospitals have assessed their own protocols and it has shown to be safe and effective. Nevertheless, the measurements of safety and effectiveness are differed among hospital protocols. Besides, the assessments were involved small sample sizes, were retrospective in nature and had non-homogenous patient populations (Hijazi & Al-Ansari, 2005; Couture *et al.*, 2013; Ajewole *et al.*, 2020).

Premixed formulations incorporated in these guidelines are meant to reduce the risk of medication errors as error rates of premixes were suggested to be lower than compounded intravenous medications (Ruble, 2008). Reports on errors associated with concentrated potassium chloride injection included incorrect identification of the product, incorrect reconstitution and unintentional bolus administration (Reeve, Allinson & Stevens, 2005; Institute for Safe Medication Practices, 2021). Premixed formulations are able to mitigate these risks by eliminating the need to reconstitute and prevent unintentional bolus administration (Nazzal & Kastango, 2018; International Medication Safety Network, 2019). Barras *et al.* reported a significant reduction of potassium chloride injection-related incidents after introducing premixed formulations along with other safety systems in their hematology ward (Barras *et al.*, 2014). Currently, to the best of our knowledge, there are no published studies on the effectiveness or safety of premixed potassium chloride. However, studies on other premixed drugs such as premixed dobutamine and premixed immunoglobulin have shown that they were comparable to the concentrated formulations (Van Der Linden *et al.*, 2002; Kallenberg, 2007). Subsequently, small scale studies have been carried out to evaluate the cost implications on the use of various premixes in hospitals (Flynn, Pearson & Barker, 1997; Van Der Linden *et al.*, 2002; Kallenberg, 2007). Results from these studies have shown that premixes are able to reduce waste, material costs and staffing needs (Witte, Eck & Vogel, 1985; Flynn, Pearson & Barker, 1997; Van Der Linden *et al.*, 2002; Kallenberg, 2007; Ruble, 2008).

1.3 Problem Statement

Treatment of hypokalaemia with intravenous potassium chloride is a complex process as many factors can affect potassium homeostasis (Kardalas *et al.*, 2018). The variations in literature and available guidelines on hypokalaemia treatment poses a challenge to physicians in making decisions. Senninger *et al.* demonstrated that there was a lack of coherence between what is being taught to medical students and available guidelines of dyskalaemia (Senninger *et al.*, 2021). The knowledge on dyskalaemia treatment was also found to be highly variable among medical students (Senninger *et al.*, 2021). In Malaysia, guidelines on hypokalaemia treatment are lacking. Potassium treatment is mentioned in a small section on diabetic ketoacidosis in the Malaysian Clinical Practice Guideline on Diabetes Mellitus (Malaysian Ministry of Health, 2015). A more informative guideline is only available in the Critical Care Handbook by the Pharmaceutical Services Division which may not be applicable in general situations (Malaysian Ministry of Health Pharmaceutical Services Division, 2013). Also, currently there are no studies on evaluating or describing the prescribing practice on this topic in Malaysia. Adverse drug reports by the National Pharmaceutical Regulatory Agency revealed no incidence of hyperkalaemia from intravenous potassium supplementation, unlike being reported up to 58% in other countries (Rimmer, Horn & Gennari, 1987; Uijtendaal *et al.*, 2011; Malaysian National Pharmaceutical Regulatory Agency, 2019a, 2020). Meanwhile, a private hospital in Malaysia reported hyperkalaemia occurred in 16.7% of cases that used concentrated potassium chloride injection (Melissa & Azmi, 2013). Therefore, the absence of reports may be due to under reporting of the adverse drug events (Abu & Shafie, 2018).

International standards recommend the incorporation of premixed or ready-to-use formulations in these guidelines to reduce the risk of medication errors associated with concentrated potassium chloride injections (Institute for Safe Medication Practices, 2017; International Medication Safety Network, 2019). In Malaysia, the concentrated form of potassium chloride injection is mostly used but medication incidents associated with its use is not known (Malaysian National Pharmaceutical Regulatory Agency, 2020). This again, may be under reported. However, a survey in a local university hospital revealed that 35% of their nurses are not aware that intravenous potassium should never be administered as bolus (Shamsuddin & Shafie, 2012). This is a grave concern as bolus administration of potassium can lead to death within minutes (Reeve, Allinson & Stevens, 2005).

1.4 Justification of Study

1.4.1 Implementing a guideline on intravenous potassium supplementation in the treatment of hypokalaemia

With the above-mentioned issues in section 1.3, there is a need to assess the current practices of hypokalaemia treatment in Malaysian hospitals. Baseline data from this study can further help in the development of a practical guideline on intravenous potassium supplementation in the treatment of hypokalaemia. Within the context of risks associated with intravenous potassium supplementation and variations existing in available guidelines, our institution (Normah Medical Specialist Centre) identified a need to have a practical or a general guideline that can be used under different conditions, which can assist prescribers in treating hypokalaemia with confidence. In order to achieve this, empirical dosing at different levels of hypokalaemia and forcing functions is required in the guideline. Evidence of safety and effectiveness of this guideline is also essential.

1.4.2 Incorporating premixed formulations in intravenous potassium supplementation

In order to develop a guideline on potassium chloride intravenous supplementation which emphasizes on premixed formulations, there is a need to evaluate the views of doctors on premixed formulations. Besides safety and effectiveness data of this formulation, an insight on the cost implications of using these premixed formulations compared to concentrated formulations is required. It is hoped that with evidence of effectiveness, safety and pharmacoeconomic data, the use of premixes would be more popular in Malaysia in the interest of patient safety.

1.5 Research Hypothesis

This research was divided into two phases and below are the research hypothesis for each phase of the study.

1.5.1 Phase 1: A Nationwide Survey on Malaysian Hospital Physicians' Use of Potassium Chloride Injection and Views on Premixed Formulation in The Treatment of Hypokalaemia

The null hypothesis (H0) of this research is:

There are no variations in the Malaysian hospital physicians' practices of potassium chloride in intravenous supplementation of potassium in hypokalaemia patients.

Physicians are not in favour of using premixed formulation in the treatment of hypokalaemia.

The alternative hypothesis (H1) of this research is:

1. There are variations in the Malaysian hospital physicians' practices of potassium chloride in intravenous supplementation of potassium in hypokalaemia patients.

2. Physicians are in favour of using premixed formulation in the treatment of hypokalaemia.

1.5.2 Phase 2: Development and Evaluation of a Guideline on Potassium Chloride Intravenous Supplementation: Effectiveness, Safety and Cost Implications

The null hypothesis (H0) of this research is: There is no difference in effectiveness, safety and cost implications between the concentrated formulation and the premixed formulation that is used based on the developed guideline on potassium chloride intravenous supplementation.

The alternative hypothesis (H1) of this research is: There is difference in effectiveness, safety and cost implications between the concentrated formulation and the premixed formulation that is used that is used based on the developed guideline on potassium chloride intravenous supplementation.

1.6 Study Objectives

Below are the objectives for each phase of the study:

1.6.1 Phase 1: A Nationwide Survey on Malaysian Hospital Physicians' Use of Potassium Chloride Injection and Views on Premixed Formulation in the Treatment of Hypokalaemia

i. Primary objective

a. To evaluate the Malaysian hospital physicians' practices of potassium chloride in intravenous supplementation of potassium in hypokalaemia patients.

ii. Secondary objective

a. To evaluate the Malaysian hospital physicians' views on using premixed formulation in intravenous supplementation of potassium in hypokalaemia patients.

1.6.2 Phase 2: Development and Evaluation of a Guideline on Potassium Chloride Intravenous Supplementation: Effectiveness, Safety and Cost Implications

i. Primary Objective:

a. To assess the safety of the premixed potassium chloride injection formulation used based on the developed guideline in a clinical setting as compared to conventional concentrated formulation in the treatment of hypokalemia.

ii. Secondary Objectives:

a. To develop a guideline on potassium chloride intravenous supplementation based on current practices in Malaysia and current international standards.

b. To assess the effectiveness of the premixed potassium chloride injection formulation used based on the developed guideline in a clinical setting as compared to conventional concentrated formulation in the treatment of hypokalemia.

c. To assess the cost implications associated with the use of premixed potassium chloride intravenous formulations as compared to the conventional concentrated formulation in the treatment of hypokalaemia.

1.7 Overview of the Thesis

Chapter 2 of this thesis consist of literature review which starts off with a general introduction of hypokalaemia and its etiology. A brief discussion on potassium replacement in hypokalaemia is included, emphasizing on the details of intravenous replacement. This includes a review on the potassium dose and rate of infusion commonly used in potassium replacement, concentration of final solution and diluent used in the preparation of potassium injection, infusion route used and monitoring parameters in potassium replacement. It continues with a discussion on the risks associated with intravenous supplementation, highlighting on

hyperkalaemia and medication error. It finishes off with a review on the available strategies to reduce the risks associated with intravenous potassium replacement in the treatment of hypokalaemia.

Chapter 3 presents the details of methodology used in the two phases of this study. The first part of the study consists of a survey carried out to evaluate the Malaysian hospital physicians' use of potassium chloride in intravenous supplementation of potassium in hypokalaemia patients and their views on premixed formulations. The second part of the study involves the development and evaluation of a guideline on potassium chloride intravenous supplementation which is divided into three parts: pre-implementation guideline part, guideline development part and post-implementation guideline part.

Chapter 4 presents the findings of the conducted nationwide survey on Malaysian hospital physicians' use of potassium chloride in intravenous supplementation of potassium in hypokalaemia patients and their views on premixed formulations. Chapter 4 also provides the findings of the pre-implementation guideline phase which involves an observational study on intravenous potassium supplementation in the treatment of hypokalaemia in a local 130-bed private hospital, solely using the concentrated formulation. This chapter subsequently presents the findings of the implemented guideline on safety, effectiveness, and cost implications in the same institution with emphasis of the use of premixed formulation. **Chapter 5** discusses on the development of the guideline based on literature review, findings from the conducted nationwide survey and observational study of the pre-implementation guideline phase.

Chapter 6 concludes the thesis with an overall conclusion of the study, recommendations for further research and limitations of the study.

1.8 Operational Definition

Hypokalaemia: Serum potassium levels below 3.5 mmol/litre

Normokalaemia: Serum potassium levels between 3.5 mmol/litre to 5.0 mmol/litre

Hyperkalaemia: Serum potassium levels above 5.0 mmol/litre

Concentrated potassium chloride injection: 1 gram /10 ml potassium chloride injection which requires reconstitution or dilution before use.

Premixed potassium chloride injection: A ready-to-use formulation of potassium chloride injection which does not require further reconstitution or dilution before use.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Potassium is an important cation in the body, mostly found in skeletal and cardiac muscles (Rastergar & Soleimani, 2001; Schaefer & Wolford, 2005). It is estimated that the total body potassium is 50 mEq/kg, with majority of this cation in the intracellular compartment (98%) compared to the extracellular compartment of the human body (2%) (Rastergar & Soleimani, 2001; Schaefer & Wolford, 2005). The concentration gradient between these two compartments determines the resting membrane potential of cells, which is responsible for the contractions of muscles (Rastergar & Soleimani, 2001; Schaefer & Wolford, 2005). Due to this, serum potassium levels are tightly regulated between 3.5-5.0 mmol/litre through various mechanisms. Acute regulation is achieved by potassium shifts between intracellular and extracellular compartments which are influenced by insulin, catecholamines, aldosterone, acid-base changes and osmolality (Rastergar & Soleimani, 2001). Long term regulation is maintained by the kidneys where potassium excretion occurs at the collecting duct (Rastergar & Soleimani, 2001).

Hypokalaemia is defined as a derangement of serum potassium of below 3.5 mmols/litre (Paice *et al.*, 1983; Alfonzo *et al.*, 2006). Causes of hypokalaemia include potassium loss from the body and transcellular shifts (Alfonzo *et al.*, 2006). Evaluation of hypokalaemia generally involves assessing urinary potassium excretion and acid-base status (Figure 2.1) (Kardalas *et al.*, 2018). Urinary potassium excretion of more than 15 mmols per day indicates renal potassium loss while below 15 mmols per day indicates non-renal losses (Kardalas *et al.*, 2018). Renal potassium losses can occur in conditions such as hypomagnesemia, renal disorders (renal tubular disorders,

Bartter's Syndrome, Liddle's Syndrome, Gitelman's Syndrome, nephrogenic diabetes insipidus) and endocrine disorders (hyperaldosteronism, Cushing's Syndrome, Conn's Syndrome) (Alfonzo *et al.*, 2006; Kardalas *et al.*, 2018). Non-renal losses can be of gastrointestinal origin such as diarrhoea and vomiting, potentiated by drugs such as diuretics, penicillin antibiotics and steroids (Alfonzo *et al.*, 2006; Kardalas *et al.*, 2018). Shifts of potassium into the cells results from stimulation of the cell's Na-K-ATPase pump which can occur from insulin or glucose therapy, beta-adrenergic stimulation (e.g. salbutamol) and alkalosis (Alfonzo *et al.*, 2006; Foringer, Norris & Finkel, 2011).

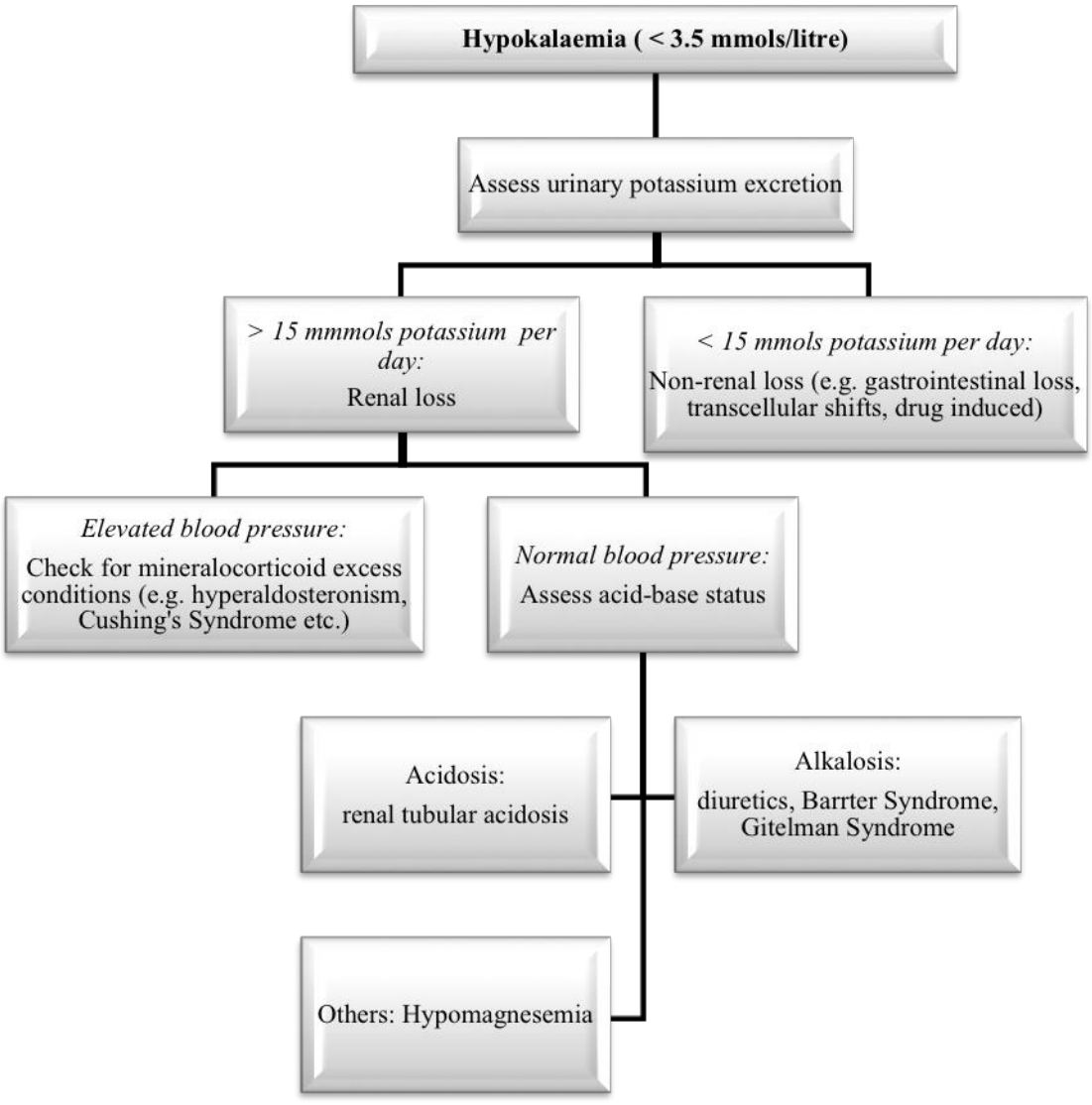

Figure 2.1 Diagnostic Evaluation of Hypokalaemia

Changes to the concentration gradient of potassium between intracellular and extracellular compartments results in the manifestation of hypokalaemia symptoms (Schaefer & Wolford, 2005). Hyperpolarization of cell membranes resulting from a drop of extracellular potassium concentration causes disruption of muscular contractions, leading to symptoms that are muscle and cardiovascular-related (Kraft *et al.*, 2005; Schaefer & Wolford, 2005). Muscle weaknesses can include fatigue, body cramps, tetany, rhabdomyolysis and respiratory failure (Alfonzo *et al.*, 2006; Foringer, Norris & Finkel, 2011). Cardiovascular symptoms include cardiac arrhythmias and ECG changes of ST segment depression, flattened T waves and presence of U waves (Alfonzo *et al.*, 2006; Foringer, Norris & Finkel, 2011).

In clinical practice, hypokalaemia is a common electrolyte abnormality (Paice *et al.*, 1983; Schaefer & Wolford, 2005). The occurrence of hypokalaemia has been reported from 6% to 20% of hospitalized patients (Paice *et al.*, 1986; Crop *et al.*, 2007; Eliacik *et al.*, 2015). Other studies on hypokalaemia incidences in hospital setting observed that majority (71%) of hypokalaemia cases were hospital-acquired, and 5% to 56% of patients develop moderate to severe hypokalaemia (Paice *et al.*, 1986; Crop *et al.*, 2007; Reid, Jones & Isles, 2012). Serum potassium in hospitalized patients are mostly influenced by comedication and patient's comorbidities (Henz *et al.*, 2008). Common factors identified include potassium renal loss and gastrointestinal loss (Reid et al, 2012, Eliacik et al., 2015, Foringer et al., 2009). Drug-induced hypokalaemia, mainly diuretics, occur about 36% to 56% of hypokalaemia cases in hospitals (Paice *et al.*, 1986; Crop *et al.*, 2007; Reid, Jones & Isles, 2012). Other causes of hypokalaemia in hospitalized patients are hyperaldosteronism, alkalosis, hypomagnesemia and other drug-inducing hypokalaemia (e.g. insulin, steroids) were less common (Paice *et al.*, 1986; Eliacik *et al.*, 2015).

Low serum potassium levels are of clinical importance as it can be life-threatening. As potassium gradient between intracellular and extracellular determines the resting potential of cell membrane, a small decrease in extracellular potassium can have detrimental effects in the heart and skeletal muscles (Clausen, 2010; Kjeldsen, 2010). It can be a trigger to arrhythmia and lead to sudden cardiac death. Skeletal muscle weaknesses seen in severe hypokalaemia can result in diaphragm muscle paralysis leading to respiratory arrest (Asmar, Mohandas & Wingo, 2012). Patients with hypokalaemia at admission have been reported to have higher mortality and length of stay compared to normokalaemic patients (Conway *et al.*, 2015). It has also been found that hypokalaemia in patients with cardiovascular problems have increased risk of arrhythmias and have a higher mortality rate (Cohn *et al.*, 2000; Goyal *et al.*, 2012).

2.2 Potassium replacement in the treatment of hypokalaemia

Potassium replacement is the basic treatment for hypokalaemia and its salt, potassium chloride, is used due to its rapid effectiveness in potassium depletion and is especially preferred in chloride-responsive metabolic alkalosis (Paice *et al.*, 1986; Gennari, 1998; Asmar, Mohandas & Wingo, 2012). In hospitalized patients, treatment of hypokalaemia is usually initiated when blood tests reveal a potassium level of below 3.5 mEq/L and depends on the clinical state of the patient. Hypokalaemia levels are categorized by serum levels as mild (3.0-3.4 mmol/litre) , moderate (2.5-2.9 mmol/litre) and severe (below 2.5 mmol/litre) (Schaefer & Wolford, 2005; Alfonzo *et al.*, 2006). Symptoms are usually absent in mild hypokalaemia and usually do not require immediate correction (Schaefer & Wolford, 2005; Alfonzo *et al.*, 2006; Kardalas *et al.*, 2018). However symptoms can be potentiated in cardiac patients or if

the serum levels falls rapidly (Schaefer & Wolford, 2005; Kardalas *et al.*, 2018). Symptoms tend to be more severe as serum levels falls and urgent correction is usually warranted in moderate to severe hypokalaemia or if patients presents with electrocardiogram (ECG) changes, arrhythmias, severe weaknesses or paralysis (Schaefer & Wolford, 2005).

Potassium replacement can be done orally or intravenously, depending on the clinical state of the patient, symptoms and severity of hypokalaemia (Weiner & Wingo, 1997; Kardalas *et al.*, 2018). Oral administration is used in asymptomatic patients and in those who can tolerate orally while the intravenous (IV) route is reserved in those who cannot take orally and for conditions that require rapid replacement such as severe hypokalaemia and patients presenting with ECG changes or muscle spasms (Paice *et al.*, 1986; Kardalas *et al.*, 2018). However, it is a common practice that IV administration is used in mild to moderate hypokalaemia cases. This may be due to a perception that IV administration has superior efficacy than the oral route or simply due to the convenience of an available IV access (Weiner & Wingo, 1997).

2.2.1 Dosage and rate of infusion of intravenous potassium in the treatment of hypokalaemia

The amount of potassium needed in the treatment of hypokalaemia is difficult to determine as there are many factors that affect the regulation of potassium balance. Body stores and distribution of potassium is regulated by different hormones, the clinical state of the patient as well as drugs taken by the patient (Gennari, 1998; Reid, Jones & Isles, 2012). It is estimated a fall of 0.3 mmol per litre represents a deficit of 100 mmol potassium total body stores (Gennari, 1998; Rastergar & Soleimani, 2001). A more recent update on hypokalaemia states that every fall of 1 mmol per litre

represents a deficit of 200 - 400 mmol potassium total body stores (Kardalas *et al.*, 2018). Studies looking into dose-response of potassium intravenous supplementation have shown that an administration of 20 mmol of potassium chloride per hour in hypokalaemic patients increases serum potassium levels by 0.5 mmol per litre (Hamill *et al.*, 1991; Kruse *et al.*, 1994). However, Chalwin *et al.* reported that an infusion of 20 mmol of potassium chloride per hour only increases serum levels by 0.22 mmol per litre and swings of potassium levels were seen during infusion and post-infusion of intravenous potassium chloride (Chalwin *et al.*, 2012). Due to limited evidence, dosing of potassium supplementation is mostly done empirically guided by serum potassium levels (Kraft *et al.*, 2005).

Dosing on intravenous supplementation of potassium in hypokalaemia are available in literature and some hospitals or institutions have come up with guidelines for their own use. Table 2.1 summarizes the available hospital or institution guidelines on intravenous supplementation of potassium. Literature recommendation on hypokalaemia treatment for intravenous supplementation of potassium in hypokalaemia range between 20 - 80 mmol potassium chloride per hour with close monitoring of potassium serum levels (Weiner & Wingo, 1997; Schaefer & Wolford, 2005; Alfonzo *et al.*, 2006). Some recommendations advice no more than 60-80 mmol is allowed before a potassium serum checking (Kraft *et al.*, 2005; Asmar, Mohandas & Wingo, 2012). Total potassium dose per day has been recommended between 75 mmols to 400 mmols per day (The Alfred Hospital, 2003; Kraft *et al.*, 2005; Ballarat Health Services, 2014; Northern Sydney Local Health District, 2014; Kardalas *et al.*, 2018). The summary of product characteristics of potassium chloride 0.15% concentrated injection recommends a maximum dose of 2-3 mmol/kg within 24 hours with a calculation formula as below (electronic medicines compendium, 2020):

mmol potassium = body weight (kg) x 0.2 x 2 x (4.5 – actual serum potassium (mmol))

Intravenous potassium are usually initiated between doses of 10 – 40 mmol (Foringer, Norris & Finkel, 2011; Viera & Wouk, 2015). Dosage recommendations for intravenous supplementation of potassium also depend on the level of hypokalaemia and presence of symptoms. Treatment would be more aggressive as the degree of hypokalaemia and symptoms gets more severe (Vanholder, Van Biesen & Nagler, 2019). Kardalas *et al.* recommends 75 mmol of potassium per day for mild hypokalaemia, 100 mmol for moderate hypokalaemia and no maximum dosing in severe hypokalaemia. Literature recommendations for empirical doses of intravenous supplementation of potassium in mild to moderate hypokalaemia range between 20 – 40 mmol and in severe hypokalaemia range between 40 – 80 mmols (Kraft *et al.*, 2005; UK Medicines Information, 2020). Available hospital guidelines vary in dosing where empirical dosing range between 10 – 40 mmols for mild hypokalaemia and 10mmols-80mmol for moderate to severe hypokalaemia (Table 2.1).

Intravenous potassium is generally recommended to be infused at a rate of 10 mmols - 20 mmols per hour, guided by serum levels and severity of symptoms (Weiner & Wingo, 1997; Rastergar & Soleimani, 2001; Kraft et al., 2005; Kardalas et al., 2018; Vanholder, Van Biesen & Nagler, 2019). Available institutional guidelines recommend infusion rates for mild to moderate hypokalaemia range between over 2 – 8 hours while for severe hypokalaemia range between over 1 – 4 hours (Table 2.1). The maximum infusion rate of 20 mmol per hour for intravenous potassium supplementation is set due to risks associated with rapid infusion (e.g. pain, phlebitis, hyperkalaemia, cardiac arrest) (Kraft et al., 2005; Alfonzo et al., 2006; Unwin, Luft & Shirley, 2011). Infusion of 20 mmols of potassium over an hour has safely increased

serum levels by 0.25 mmols in an intensive care setting (Kruse et al., 1994; Asmar, Mohandas & Wingo, 2012). However, higher infusion rates have been recommended in special circumstances. Recommendations of infusion rates of 40 mmols/hour and above should be reserved in critical and symptomatic situations (Kraft et al., 2005; Foringer, Norris & Finkel, 2011). Experiences on using fast infusion rates of up to 100 mmols per hour also have been documented in life-threatening situations such as in fatal arrhythmias and imminent cardiac arrest (Choy et al., 1997; American Heart Association, 2000; Welfare, Sasi & English, 2002; Foringer, Norris & Finkel, 2011). Most available institutional guidelines set maximum infusion rates between 20 – 40 mmols/hour (Table 2.1). Due to the risks associated with fast infusion rates, infusion rates of 10 – 20 mmol per hour and above would require cardiac monitoring and a central vein access and this is also reflected in available institutional guidelines (Table 2.1) (Kraft et al., 2005; Foringer, Norris & Finkel, 2011; Asmar, Mohandas & Wingo, 2012).

2.2.2 Concentration of reconstituted potassium solution and diluent used for reconstitution

Potassium chloride injection mostly comes in the concentrated form (1 g per 10 ml injection or 15%) which needs to be diluted before administration (electronic medicines compendium, 2020). The standard dilutions are available in 20 mmols to 40 mmols in one litre of diluent (Asmar, Mohandas & Wingo, 2012; Viera & Wouk, 2015). Pain and phlebitis is a concern with high concentrations of potassium injections (Asmar, Mohandas & Wingo, 2012; Vanholder, Van Biesen & Nagler, 2019). However, it is needed in certain situations. Some patients such as renal impairment patients, congestive heart failure patients and ventricular impaired patients may not be able to tolerate large amounts of fluid and a more concentrated preparation is needed

(Foringer, Norris & Finkel, 2011; Asmar, Mohandas & Wingo, 2012). A concentration of up to 200 mmol/L was shown to be well tolerated, improved symptoms and did not cause hyperkalaemia (Kruse *et al.*, 1994). Most institutional guidelines set maximum concentrations of 40 mmol/litre (Table 2.1). However, higher concentrations would require additional monitoring (Table 2.1).

Ideally, concentrated potassium chloride is diluted in saline solutions (e.g. 0.9% sodium chloride) (Kraft *et al.*, 2005; Kardalas *et al.*, 2018; electronic medicines compendium, 2020). Other compatible diluents are dextrose solutions but these can cause an increase in insulin serum levels which lead to a shift of potassium from the extra- to the intracellular space leading to lower serum potassium (Weiner & Wingo, 1997; Kraft *et al.*, 2005; Kardalas *et al.*, 2018). It has been documented as a cause of inadequate potassium supplementation (Chen *et al.*, 2012).

2.2.3 Infusion route

Potassium injections can be administered through the peripheral or central vein. Due to the caustic nature of potassium solutions, the peripheral line is usually limited to concentrations of 40 mmols/litre (Kruse *et al.*, 1994; Asmar, Mohandas & Wingo, 2012; UK Medicines Information, 2020). Some recommend higher limits of 80 mmols/litre for peripheral lines where a larger peripheral line may be needed (Kraft *et al.*, 2005; Gloucestershire Hospitals, 2010; University Hospitals of Leicester, 2019). Rates of above 10 mmol/hour would also require a central line (Kraft *et al.*, 2005; Asmar, Mohandas & Wingo, 2012). A central line would be able to avoid infusion-related side effect from high concentration of potassium solutions and high infusion rates. Nevertheless, variation exist on the recommendations of the infusion route (see Table 2.1).

2.2.4 Monitoring of intravenous potassium supplementation

Monitoring the effectiveness and safety of intravenous supplementation of potassium mainly involves taking timely serum potassium levels and cardiac monitoring when necessary. Serum potassium levels are taken to monitor the effectiveness of potassium replacement, though it is not representation of total body potassium (Cohn *et al.*, 2000). Any decrease in serum potassium level would cause cells to release potassium into the extracellular fluid to compensate the deficit (Unwin, Luft & Shirley, 2011). A decrease of 0.3 mmol/litre of serum potassium is estimated to represent a decrease of 100 mmol of total body potassium stores (Gennari, 1998; Rastergar & Soleimani, 2001). Frequency of serum potassium levels monitoring would be more as the levels get more severe or the patients experiences severe symptoms (Kraft *et al.*, 2005; Kardalas *et al.*, 2018). Daily serum potassium monitoring is generally recommended for asymptomatic patients with mild to moderate hypokalaemia (Kraft *et al.*, 2005; Kardalas *et al.*, 2018). Frequent serum potassium monitoring is needed in severe and symptomatic patients (Kraft *et al.*, 2005; Alfonzo *et al.*, 2006; Kardalas *et al.*, 2018). Severe hypokalaemic patients presenting with or without cardiac symptoms (e.g. arrhythmias) are recommended to have serum levels checked every 2 – 4 hours (Asmar, Mohandas & Wingo, 2012). In an intensive care setting, serum monitoring is recommended to be checked every 1-6 hours for symptomatic severe hypokalaemia patients while for mild to moderate hypokalaemia, monitoring is done within 2 – 8 hours with daily monitoring (Kraft *et al.*, 2005). Available institution guidelines show variations in the frequency of serum level checking (Table 2.1).

Continuous cardiac monitoring is recommended in fast correction of hypokalaemia due to the risk of arrhythmia or cardiotoxicity (Alfonzo *et al.*, 2006; Asmar, Mohandas & Wingo, 2012; Vanholder, Van Biesen & Nagler, 2019; UK Medicines Information, 2020). Usually cardiac monitoring is needed in severe hypokalaemia as patients would be symptomatic and fast repletion is necessary (Kardalas *et al.*, 2018). In fast repletion of potassium, higher concentrations of potassium solutions and higher rates of infusions are needed. Recommendations have set cardiac monitoring is required in concentrations higher than 40 mmol/litre to 80 mmol/litre ((Meredith, 2006; Irish Medication Safety Network, 2013; Northern Sydney Local Health District, 2014)). The rates of infusion where cardiac monitoring is required vary between 10 mmol/hour to 20 mmol/hour (Kraft *et al.*, 2005; Asmar, Mohandas & Wingo, 2012; UK Medicines Information, 2020). According to the currently available institutional guidelines, the rates were varied between 10 mmol/hour to 40 mmol/hour (Table 2.1). Some guidelines recommend cardiac monitoring whenever a central line is used due to cardiotoxicity (Kruse *et al.*, 1994; East Cheshire Trust, 2015; UK Medicines Information, 2020).

Table 2.1 Available Institutional Guideline Online on Intravenous Supplementation of Potassium

Institution Guideline	**Dosage of Potassium**	**Maximum Concentration of Final Solution**	**Maximum Rate of Infusion**	**Recommended Monitoring**
Orlando Regional Medical Centre (Orlando Regional Medical Center, 2001)	10 – 20 mmol over 1-2 hours	Peripheral line: 10 mmol/50 ml Central line: 20 mmol/50 ml	20 - 40 mmol per hour	Monitor serum levels 2 hours after infusion complete ECG monitoring if maximum rates are used
Nottingham City Hospital (Nottingham City Hospital, 2002)	Maximum dose: 200 - 300 mmol (3 mmol/kg/day)	Peripheral line: 80 mmol/litre	Peripheral line: 40 mmol per hour	Serum levels after every 80 mmol dose ECG monitoring for rates above 10 mmol per hour
Thomas Jefferson University Hospital (Thomas Jefferson University Hospital, 2002)	Mild hypokalaemia: 20 mmol x4 doses Moderate hypokalaemia: 20 mmol x6 doses Severe hypokalaemia: 20 mmol x8 doses	Not stated	Not stated	Serum levels 2 hours after 4^{th} – 6^{th} dose Cardiac monitoring for rates above 20 mmol per hour
The Alfred Hospital (Vreede *et al.*, 2005)	Mild hypokalaemia: 90 mmol over 24 hours Moderate to severe hypokalaemia: 10 – 40 mmol per hour	Peripheral line: 10 mmol per 100 ml	Peripheral line: 10 mmol per hour	ECG monitoring and frequent serum monitoring if infusion rates are above 10 mmol per hour
Royal North Shore & Ryde Hospital Pharmacy Guidelines (Meredith, 2006)	30 mmol, maximum dose 200 mmol in 24 hours	Peripheral line: 40 mmol/litre	Peripheral line: 20 mmol per hour	Serum levels every 4 - 6 hours ECG monitoring required for rate of infusion above 10 mmol/hour and concentrations above 60 mmol/litre.