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# A NATIONWIDE SURVEY ON MALAYSIAN HOSPITAL PHYSICIANS' PRACTICES OF INTRAVENOUS POTASSIUM CHLORIDE SUPPLEMENTATION AND OPINIONS ON PREMIXED FORMULATION IN THE TREATMENT OF HYPOKALAEMIA

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## ABSTRACT

*This study aims to evaluate the Malaysian hospital physicians' practices of intravenous potassium chloride in the treatment of hypokalaemia and their opinions on using premixed formulation. This was a nationwide online survey using a self-administered questionnaire. The survey link was sent to the practising hospital physicians in Malaysia through email (n = 1,455), Facebook Messenger (n = 2,734) and posted on Facebook as well. A total of 207 responses were received. The physicians were mostly males (63.8%), aged between 30 years old–39 years old (51.2%) and worked in the government sectors (76.8%). The most preferred dosage of potassium chloride for mild, moderate and severe hypokalaemia was 10 mmol (44.4%), 20 mmol (55.1%) and 30 mmol (37.7%), respectively. The mostly chosen infusion rate of potassium chloride for mild hypokalaemia was over 24 h (41.1%) while for both moderate and severe hypokalaemia were over 1 h–2 h (63.8% and 89.9%, respectively). The concentration of intravenous potassium chloride is the main factor (68.1%) which would influence the infusion route choice. Serum potassium monitoring of every 24 h was chosen by 52.7% of the respondents for mild hypokalaemia while every 1 h–2 h was mostly chosen for moderate and severe hypokalaemia (49.3% and 87.4%, respectively). Cardiac monitoring was mostly opted in severe hypokalaemic patients (70.0%). Majority of physicians agreed that a premixed formulation is easier to administer (64.7%) and safer for the patients (51.7%). In conclusion, there were variations in the prescribing practices among Malaysian physicians to treat hypokalaemia. Most physicians were in favour of premixed formulation.*

***Keywords*:** Potassium chloride injection, Hypokalaemia, Premixed formulation, Hospital physicians, Malaysia

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## INTRODUCTION

Hypokalaemia is a common electrolyte abnormality encountered in clinical practice and is defined as serum potassium of below 3.5 mEq/L (DiPiro *et al.* 2020). A retrospective study revealed that approximate 20% of hospitalised patients developed hypokalaemia (Paice *et al.* 1986). Nevertheless, higher incidences have been reported in another study which showed that among 141 patients that were admitted with hypokalaemia, 71% developed hospital-acquired hypokalaemia and 40% of these patients had at least one severe episode of hypokalaemia (Crop *et al.* 2007). This common electrolyte imbalance can lead to life-threatening sequalae (Miller and Graham 2006). Potassium gradient between intracellular and extracellular determines the resting potential of cell membrane. An altered extracellular potassium level can have detrimental effects to the heart muscles. Thus, hypokalaemia can trigger arrhythmia and lead to sudden cardiac death (DiPiro *et al.* 2020).

Potassium replacement is the basic treatment for hypokalaemia. Its salt, potassium chloride is used due to its rapid effectiveness in potassium depletion and is especially preferred in chloride-related hypokalaemia caused by diarrhoea and diuretics use (DiPiro *et al.* 2020). In hospitalised patients, treatment of hypokalaemia is usually initiated when serum potassium level is below 3.5 mEq/L. Electrolyte replacement can be done either orally or intravenously, depending on the clinical state of the patient, symptoms and severity of hypokalaemia (Weiner and Wingo 1997). Oral administration is used in asymptomatic patients and in those who can tolerate orally. Whereas, the intravenous route is reserved for conditions requiring rapid replacement such as severe hypokalaemia, patients presenting with electrocardiogram (ECG) changes or muscle spasms and those who cannot tolerate orally (DiPiro *et al.* 2020).

Intravenous potassium repletion is usually guided by close monitoring of serum potassium levels. Owing to the risks associated with intravenous potassium supplementation, several institutions have implemented guidelines on potassium replacement (Irish Medication Safety Network 2013; Royal North Shore & Ryde Hospital 2006; University Hospital of Leicester NHS Trust 2018). With a narrow normokalaemic range of 3.5 mmol/L to 5.1 mmol/L, hyperkalaemia is a grave concern in intravenous potassium supplementation, especially when the rate of potassium supplementation overwhelms intracellular shifts and renal excretion (Rastergar and Soleimani 2001). There were reports of hyperkalaemia from intravenous potassium supplementation and approximate 50% of hyperkalaemia episodes were due to supplemental potassium chloride (Koda Kimble *et al*. 2009; Rimmer, Horn and Gennari 1987). Despite the common occurrence of hypokalaemia in hospital setting, there is no general consensus regarding the dose, concentration, rate, duration, route of potassium chloride injection or how rapid potassium correction should be administered in hypokalaemia treatment (Singhi, Gautham and Lal 1994). Although therapeutic guidelines on intravenous potassium supplementation are available in numerous institutions, they display variations and its effectiveness and safety have not been thoroughly evaluated (Irish Medication Safety Network 2013; University Hospital of Leicester NHS Trust 2018).

Medication errors is another concern with intravenous potassium chloride supplementation. The concentrated form of potassium chloride injection (1 g potassium chloride in 10 mL) is usually used in intravenous supplementation of potassium. It is a high alert drug which can cause serious harm when misused (Joint Commission on Accreditation of Healthcare Organizations 2001). This concentrated form of potassium chloride injection, which is to be diluted before administration has been associated with fatal medical errors. In these fatal cases, hyperkalaemia and abnormal ECG changes leading to ventricular fibrillation and cardiac arrhythmia were seen (Wetherton *et al*. 2003). Besides, intravenous potassium supplementation is a complex process with many opportunities of error such

as administering intravenous potassium with inappropriate potassium levels and incorrect preparation or dilution (Argo, Cox and Kelly 2000).

Implementing clear guidelines can ensure the safety and efficacy of potassium intravenous supplementation. The availability of therapeutic guidelines has shown to reduce medication incidents (Barras *et al*. 2014; Tubman *et al.* 2005). Treatment guidelines in hospitals are recommended to be developed by the institution's Pharmacy & Therapeutics Committee. The guidelines should include multiple forcing functions such as maximum concentration, rate of infusion, dosage limits and patient monitoring (Barras *et al*. 2014; Tubman *et al.* 2005). Besides, several studies encouraged the use of premixed formulations whenever possible to reduce the use of the concentrated formulations due to the risk of medication errors (Barras *et al*. 2014; Tubman *et al.* 2005). Premixed formulations eliminate the need to reconstitute before administration, thus eliminating the possible errors in wrong dilution (Barras *et al*. 2014).

In Malaysia, the concentrated form of potassium chloride which needs dilution before administration is mostly used in intravenous potassium chloride supplementation. Previously, the concentrated form is the only formulation registered in Malaysia and premixed formulations are only available through special import permit. However, in year 2017, one strength of the premixed formulation was firstly registered in Malaysia. To the best of our knowledge, only two private hospitals are currently using premixed formulation in Malaysia in the interest of improving patient safety. In order to improve the prescribing practice of intravenous potassium chloride supplementation, an overview on the current prescribing practice and opinions from physicians is essential. Therefore, this nationwide survey was aimed to assess the Malaysian hospital physicians' practices of intravenous potassium chloride supplementation in hypokalaemia. The physicians' opinions on premixed potassium chloride formulation in the treatment of hypokalaemia was assessed as well. To date, there has not been any survey being conducted on physician's practice on the treatment of hypokalaemia in Malaysia.

## METHODS

This was an online survey using a self-administered anonymous questionnaire. The questionnaire was developed based on information from literature reviews. The questionnaire consisted of three sections. The first section of the questionnaire collected physicians' demographics data. The second section focused on the physicians' current practices of intravenous supplementation of potassium in hypokalaemia treatment. The third section addressed the physicians' opinions on the use of intravenous premixed potassium chloride formulations to replace concentrated formulations.

The questionnaire was initially gone through face and content validation by three experts which were two senior academicians from School of Pharmaceutical Sciences, Universiti Sains Malaysia and one practicing nephrologist from Normah Medical Specialist Centre, Malaysia. A pilot study involved 20 physicians was conducted and adjustments were made on the questionnaire based on the feedback from the physicians. The reliability of the questionnaire was analysed by calculating Cronbach's Alpha from the responses of the pilot study. This was done for questions on rate of infusion and monitoring frequency prescribed at different levels of hypokalaemia. The Cronbach's Alpha for rate of infusion prescribed at different levels of hypokalaemia was 0.772 while for monitoring frequency prescribed at different levels of hypokalaemia was 0.800.

The study inclusion criteria was practising Malaysian physicians from both private and government hospitals in Malaysia. The physicians must have experiences in treating

hypokalaemia with intravenous potassium chloride in adult patients. The total number of physicians in Malaysia were obtained from the Ministry of Health Malaysia official portal (Ministry of Health Malaysia 2015). The total number of physicians in Malaysia during the study period were 40,646. The sample size of physicians was calculated by using the Raosoft® software. Assuming 85% of the physicians have experiences in using potassium chloride injections to treat hypokalaemia in adult patients, a total of 195 physician would provide a representative sample size with 5% margin of error and 95% confidence level. The 85% assumption was based on expert opinions from consultant specialists in Normah Medical Specialist Centre. The expert opinion was used as there was no previous study on the prevalence of physician involved in hypokalaemia treatment.

The initial sampling frame included only the physicians with their email addresses can be traced from the websites or search engines. The email addresses were obtained from hospital websites or other available online search engines of the Malaysian Medical Council, Ministry of Health Malaysia, Association of Private Hospitals Malaysia, National Specialist Register and Malaysian Medical Resources. This created a sampling frame of 1,455 physicians with email addresses. Subsequently, a total of 195 physicians were selected from the sampling frame by using simple random sampling. Invitation letters containing a URL hyperlink to the survey questionnaire were directly emailed to these 195 physicians. However, due to the poor response, several sampling frames were subsequently constructed, and random sampling was regenerated. As the target sample size was still not achieved, the questionnaire was finally sent to all the 1,455 physicians in the sampling frame.

However, the targeted sample size was not achieved after sending the questionnaire to all the 1,455 physicians. In order to further improve the response rate, the questionnaire was sent through Facebook Messenger with embedded hyperlink. Hence, another sampling frame was created which consists of physicians with the social media Facebook account. The physicians' name and profile were searched through the social media Facebook. A total of 2,734 physicians names were managed to obtain and sent with the survey hyperlink through Facebook Messenger. The survey hyperlink was also posted on the Facebook. The data was collected from February 2016 to January 2017.

Statistical analysis was performed by using Statistical Package for the Social Sciences (SPSS) version 20.0. Data from the survey was analysed descriptively and presented in frequency or percentage. This study had obtained ethical approval from the Medical Research & Ethics Committee, Ministry of Health Malaysia [Ethics Approval number: NMRR-15-578-25905 (IIR)].

## RESULTS

Upon completion of data collection, the total of valid responses was 207, whereby 157 physicians responded through Facebook Messenger (response rate 5.7%) while another 47 physicians responded via email (response rate 3.2%). The remaining three responses were received from Facebook post. The median age of the physicians was 35.5 years old (IQR: 31.00 years old–43.00 years old). The responding physicians were mostly male (63.8%) and the median years of practice of 10.00 years old (IQR: 6.00 years old–16.00 years old). Majority of the physicians (76.8%) were from the government hospitals. Most of the physicians' medical specialties included internal medicine (21.7%) and anaesthesiology (20.3%). The physicians were mainly working in the medical ward (25.2%) and intensive care unit (ICU) (23.7%) (Table 1).

**Table 1:** Demographic characteristics of physicians.

| Characteristics | *n* (%) | Characteristics | *n* (%) |
|---|---|---|---|
| Age group (years old) | | Medical specialty | |
| < 30 | 24 (11.6) | Internal medicine | 45 (21.7) |
| 30–39 | 106 (51.2) | Anaesthesiology | 42 (20.3) |
| 40–49 | 49 (23.7) | Emergency medicine | 31 (15.0) |
| 50–59 | 21 (10.1) | General surgery | 20 (9.7) |
| ≥ 60 | 6 (2.9) | Others | 57 (27.8) |
| Missing data | 1 (0.5) | Without medical specialty | 12 (5.8) |
| Gender | | Ward involved[a] | |
| Male | 132 (63.8) | Medical | 49 (25.2) |
| Female | 75 (36.2) | Intensive care unit (ICU) | 46 (23.7) |
| Years of practice | | Accident & emergency (A&E) | 36 (18.6) |
| < 5 | 22 (10.6) | Surgical | 35 (18.0) |
| 5–10 | 89 (43.0) | Anaesthesiology | 14 (7.2) |
| 11–15 | 30 (14.5) | Cardiology | 7 (3.6) |
| 16–20 | 31 (15.0) | Oncology | 6 (3.1) |
| 21–25 | 15 (7.2) | Obstetrics & gynaecology (O&G) | 6 (3.1) |
| > 25 | 18 (8.7) | Orthopaedic | 3 (1.5) |
| Missing data | 2 (1.0) | Otorhinolaryngology | 3 (1.5) |
| Current place of practice | | Neurosurgery | 3 (1.5) |
| Government hospital | 159 (76.8) | Others | 26 (13.0) |
| Private hospital | 47 (22.7) | Missing data | 1 (0.5) |
| Missing data | 1 (0.5) | | |

*Note*: [a]The number of wards involved were more than 207 as some physicians worked in more than one ward.

The physicians were enquired on their experiences in using type of intravenous potassium chloride formulation. More than three quarters (76.8%) of the physicians had experiences in using only the concentrated formulation. Meanwhile, 23.2% physicians had previously used the premixed formulation. For the dosage selection in mild hypokalaemia, most of the physicians (44.4%) opted for 10.0 mmol of potassium chloride supplementation. Meanwhile, in moderate hypokalaemia, slightly more than half of the physicians (55.1%) chose 20.0 mmol of potassium chloride supplementation. The 30.0 mmol potassium chloride supplementation was the most selected dosage by the physicians (37.7%) for severe hypokalaemia. Considering different rates of infusion, majority of the physicians (41.1%) preferred to administer potassium chloride over 24 h for mild hypokalaemia. Whereas, the 1 h–2 h rate of infusion were set for moderate and severe hypokalaemia by 63.8% and 89.9% of physicians, respectively (Table 2).

**Table 2:** Prescribing practices of intravenous potassium chloride supplementation (types of formulation, dosage and rate of infusion).

| Question | *n* (%) |
|---|---|
| 1. Which formulation of intravenous potassium chloride do you use during your practice? | |
| Concentrated formulation | 159 (76.8) |
| Premixed formulation or ready-to-use formulation | 35 (16.9) |
| Both types of formulations | 13 (6.3) |
| 2. What is the dosage of intravenous potassium chloride you would normally administer to patients with the following serum potassium levels? | |
| 2(a). Dosage in mild hypokalaemia (3.0 mmol/L–3.4 mmol/L): | |
| 10.0 mmol | 92 (44.4) |
| 20.0 mmol | 25 (12.1) |
| Others dosage | 8 (4.0) |
| IV treatment not indicated | 77 (37.2) |
| Missing data | 5 (2.4) |
| 2(b). Dosage in moderate hypokalaemia (2.5 mmol/L–2.9 mmol/L): | |
| 20.0 mmol | 114 (55.1) |
| 30.0 mmol | 32 (15.5) |
| 40.0 mmol | 14 (6.8) |
| Others dosage | 36 (17.4) |
| IV treatment not indicated | 4 (1.9) |
| Missing data | 7 (3.4) |
| 2(c). Dosage in severe hypokalaemia (below 2.5 mmol/L): | |
| 20.0 mmol | 18 (8.7) |
| 30.0 mmol | 78 (37.7) |
| 40.0 mmol | 58 (28.0) |
| Others dosage | 42 (20.4) |
| Missing data | 11 (5.3) |
| 3. What is the rate of infusion of intravenous potassium chloride you would normally administer in patients with the following serum potassium levels? | |
| 3(a). Rate of infusion in mild hypokalaemia (3.0 mmol/L–3.4 mmol/L): | |
| Over 1 h–2 h | 38 (18.4) |
| Over 24 h | 85 (41.1) |
| Others rate | 4 (2.0) |
| Intravenous treatment not indicated | 77 (37.2) |
| Missing data | 3 (1.4) |
| 3(b). Rate of infusion in moderate hypokalaemia (2.5 mmol/L–2.9 mmol/L): | |
| Over 1 h–2 h | 132 (63.8) |
| Over 24 h | 59 (28.5) |
| Others rate | 15 (7.3) |
| Missing data | 1 (0.5) |
| 3(c). Rate of infusion in severe hypokalaemia (below 2.5 mmol/L): | |
| Over 1 h–2 h | 186 (89.9) |
| Others rate | 12 (5.8) |
| Missing data | 9 (4.3) |
| 4. Under what conditions would you use a faster rate of infusion of between 1 h–2 h in mild to moderate hypokalaemia? | |
| Presence of hypokalaemia symptoms such as cardiac or muscle related symptoms | 181 (87.4) |
| Cardiac patients | 56 (27.1) |
| Critically ill patients (e.g.: post-surgery, ventilated patients, sepsis) | 6 (2.9) |
| Others | 5 (2.4) |
| Never use fast rate of infusion | 8 (3.9) |

Physicians' response on the conditions that require higher infusion rates (1 h–2 h) in mild to moderate hypokalaemia were recorded. Majority (87.4%) of the physicians opted the use of higher rates in patients presenting with the cardiac or muscle related symptoms. A total of 27.1% fixed the use of higher rate of infusion in cardiac patients (Table 2). When assessing the factors in determining choice to use a more concentrated (above 40 mmol/L) final solution, majority physicians used it for patients with symptoms of fluid overload (74.9%). Considering the use of dextrose as diluent, most physicians (85.0%) did not reconstitute concentrated potassium chloride injection with dextrose. However, a total of 29 (14.0%) physicians used dextrose diluents. More than half of the physicians would consider the concentration of the potassium chloride solution (68.1%) and the intravenous line availability (60.4%) as the factors which determine the choice of infusion route (central or peripheral line) (Table 3).

**Table 3:** Prescribing practices of intravenous potassium chloride supplementation (factors determining the use of a more concentrated intravenous potassium chloride, glucose diluent and infusion route).

| Question | *n* (%) |
|---|---|
| 1. The usual final concentration of intravenous potassium chloride for administration is between 10 mmol/L and 40 mmol/L. What are the factors that determine your choice of a more concentrated intravenous potassium chloride final concentration (e.g.: 20 mmol in 100 mL) | |
| Patients with symptoms of fluid overload | 155 (74.9) |
| Congestive heart failure patients | 113 (54.6) |
| Renal impairment patients | 81 (39.1) |
| Arrhythmic patients, severe hypokalaemia or faster correction needed | 16 (7.7) |
| Availability of central line | 6 (2.9) |
| Others | 5 (2.4) |
| Never use a more concentrated solution | 10 (4.8) |
| 2. Do you prescribe glucose diluents (e.g.: dextrose 5% solution) to reconstitute concentrated intravenous potassium chloride? | |
| Yes | 29 (14.0) |
| Yes (with reasons provided) | 7 (3.4) |
| Hypernatremia | 2 (1.0) |
| Low blood glucose | 2 (1.0) |
| Dextrose as a transportation medium | 2 (1.0) |
| To prevent arrhythmia | 1 (0.5) |
| Yes (without reasons provided) | 22 (10.6) |
| No | 176 (85.0) |
| Missing data | 2 (1.0) |
| 3. What are the factors that determine your choice of infusion route (central or peripheral line)? | |
| Concentration of intravenous potassium chloride to be administered | 141 (68.1) |
| Availability of intravenous line on patient | 125 (60.4) |
| Based on patient's conditions | 3 (1.4) |

When assessing the timing of performing serum potassium levels monitoring after the administration of intravenous potassium chloride, slightly more than half (52.7%) of the physicians monitored the levels after 24 h in mild hypokalaemic patients. Whereas, in moderate hypokalaemia, nearly half (49.3%) respondents opted to monitor patients' serum after 1 h–2 h while 34.8% of physicians preferred after 8 h–12 h. However, serum monitoring

of after 1 h–2 h was the most (87.4%) chosen frequency in severe hypokalaemic patients. There were several factors determining the need of cardiac (ECG) monitoring after the administration of potassium chloride. A total of 70.0% physicians would perform cardiac monitoring in severe hypokalaemic patients. Meanwhile, 48.8% of physicians felt the need to have cardiac monitoring in patients with infusion rates above 20 mmol/h (Table 4).

Physicians' opinions on replacing the concentrated form of potassium chloride injection with premixed formulation were taken. A total of 64.7% physicians preferred premixed formulation as it is easier to administer. Besides, about half (51.7%) of the physicians supported premixed formulation because it is a safer choice for the patients. However, a proportion of physicians disagreed with the use of premixed formulations due to the limited choices of concentration (42.0%) and inappropriateness for fluid overload patients (33.3%) (Table 4).

**Table 4:** Prescribing practices of intravenous potassium chloride supplementation monitoring and opinions on premixed formulation use.

| Question | *n* (%) |
|---|---|
| 1. How soon do you perform serum potassium levels monitoring after the administration of intravenous potassium chloride for the following levels of hypokalemia? | |
| 1(a). Serum potassium levels monitoring in mild hypokalaemia: | |
| After 24 h | 109 (52.7) |
| After 1 h–2 h | 50 (24.2) |
| After 8 h–12 h | 41 (19.8) |
| Others | 2 (1.0) |
| Missing data | 5 (2.4) |
| 1(b). Serum potassium levels monitoring in moderate hypokalaemia: | |
| After 1 h–2 h | 102 (49.3) |
| After 8 h–12 h | 72 (34.8) |
| After 24 h | 27 (13.0) |
| Others | 6 (3.0) |
| 1(c). Serum potassium levels monitoring in severe hypokalaemia: | |
| After 1 h–2 h | 181 (87.4) |
| After 8 h–12 h | 17 (8.2) |
| Others | 7 (3.5) |
| Missing data | 2 (1.0) |
| 2. When do you perform cardiac monitoring (ECG monitoring) for patients receiving intravenous potassium chloride? | |
| In severe hypokalaemic patients | 145 (70.0) |
| For infusion rates above 20.0 mmol/h | 101 (48.8) |
| For concentrations above 80.0 mmol/L | 68 (32.9) |
| For infusion rates above 10.0 mmol/h | 45 (21.7) |
| For all patients on intravenous potassium chloride | 14 (6.8) |
| Others | 13 (6.3) |
| 3. What is your opinion on replacing the concentrated form of potassium chloride injection with the premixed formulation? | |
| Premixed formulation is easier to administer | 134 (64.7) |
| Premixed formulation is safer for the patients | 107 (51.7) |
| Premixed formulation is not suitable for patients with fluid overload risks | 69 (33.3) |
| Premixed formulation has limited choice of concentration | 87 (42.0) |
| Others (e.g.: symptomatic patients, cardiac patients, cost implication, avoid miscalculation of dose) | 4 (2.0) |

## DISCUSSION

This study revealed that there were variations in prescribing practices among hospital physicians in Malaysia for the treatment of hypokalaemia with intravenous potassium chloride. According to the currently available guidelines, the dosage recommendations for potassium were ranged between 10 mmol–20 mmol for mild hypokalaemia, 10 mmol–40 mmol for moderate hypokalaemia and 20 mmol–40 mmol for severe hypokalaemia (Ballarat Health Services 2014; Gloucestershire Hospitals 2014; Kraft et al. 2005; Orlando Regional Medical Centre 2008). The preferable dosage choices of the responding physicians in this study were depending on the hypokalaemia severity. The preferred dosage of 10 mmol for mild hypokalaemia, 20 mmol for moderate hypokalaemia and 30 mmol for severe hypokalaemia, respectively, by the responding physicians in this study were consistent with the recommended dosage by the guidelines.

As potassium replacement is usually guided by signs and symptoms of the patients, the rate of infusion is usually distinct at different degree of hypokalaemia. The rate of correction is relatively slow in mild hypokalaemia patients as these patients are usually asymptomatic and fast correction is unnecessary (Gloucestershire Hospitals 2014; Rastergar and Soleimani 2001). The infusion rate of over 24 h was mostly chosen by the physicians of this study in mild hypokalaemia. However, there are some instances where a fast rate of infusion is needed in mild hypokalaemia. For example, critically ill patients who were symptomatic even with mild hypokalaemia were treated more aggressively. This is owing to the underlying conditions which predisposing critically ill patients to hypokalaemia or the patients might be receiving several drugs that can cause hypokalaemia (Kraft *et al.* 2005). This is consistent with the study response on the question of a fast infusion rate is needed in mild to moderate hypokalaemia for which majority of physicians opted for symptomatic patients. For moderate to severe hypokalaemia, a faster rate of infusion is usually needed as most patients are symptomatic at these stages (Rastergar and Soleimani 2001). Most reference and guidelines recommended a rate of infusion of over 1 h–2 h (Ballarat Health Services 2014; Gloucestershire Hospitals 2014; Kraft et al. 2005; Orlando Regional Medical Centre 2008) and this was consistent with the responses given in this study where in both moderate and severe hypokalaemia, the rate of infusion of over 1 h–2 h were mostly chosen by the physicians.

Most of the guideline recommendations include a maximum final concentration of 40 mmol/L potassium chloride solution due to the risk of infusion pain, venous sclerosis and potassium toxicity leading to ECG changes and arrhythmia (Kruse *et al.* 1994). However, potassium chloride concentrations up to 200 mmol/L have been reported to be used safely (Kruse *et al.* 1994). A more concentrated solution is usually needed for fluid overload patients or patients who need fluid restriction such as renal impairment, congestive heart failure and patients undergoing cardiac surgery. In this study, majority of physicians used a more concentrated solution for patients with fluid restrictions or patients who present with fluid overload symptoms. Other reasons stated by the responding physicians for the use of more concentrated solution were severe hypokalaemia, when faster correction is needed, available central line, liver impairment, poisoning, culprit drugs and age of patient. These reasons except for severe hypokalaemia were not found in any of the guidelines. In severe hypokalaemia, the guidelines generally recommend a more concentrated solution as faster correction is necessary and a smaller final volume is needed (East Cheshire NHS Trust 2019). A concentrated solution would also need a central line or large peripheral veins as it is sclerotic to the veins and this may have been the reason for the availability of central line (East Cheshire NHS Trust 2019; Gloucestershire Hospitals 2014). Liver impairment such as portal hypertension in cirrhosis usually presents with ascites and the elderly patients are

prone to fluid overload (Rolls and Phillips 1990). Certain drug poisonings do pose a risk of fluid overload and drugs such as steroids and calcium channel blockers can cause fluid retention (Smith 2021). Hence, it is more appropriate to use more concentrated solution in these conditions.

Sodium chloride solutions is the recommended diluent to reconstitute concentrated potassium chloride (DiPiro *et al.* 2020; Irish Medication Safety Network 2013). Meanwhile, dextrose solutions are another recommended diluent, but these solutions can cause an increase in insulin serum levels. The elevated serum level of insulin may lead to a shift of potassium from the extracellular to the intracellular space, leading to lower serum potassium, which has been documented as a cause of inadequate potassium supplementation (DiPiro *et al.* 2020; Weiner and Wingo 1997). Meanwhile, dextrose diluents are used in the current practice and guidelines do include dextrose diluents with notes on transcellular potassium shifts and preference to sodium chloride diluents (Ballarat Health Services 2014: Gloucestershire Hospitals 2014). This study revealed that although most physicians used sodium chloride diluents, there was a small percentage of physicians who use dextrose diluents for patients with hypernatremia or low blood glucose. Dextrose fluid therapy is generally indicated in these conditions (Sterns 2021).

The reconstituted form of potassium chloride injection can be administered through the central or peripheral vein. There are some circumstances where the peripheral line is to be avoided. The peripheral line is limited to a less concentrated solution as potassium chloride is sclerotic to the veins (Asmar, Mohandas and Wingo 2012). Problems arising from peripheral lines including pain, phlebitis and venous sclerosis which lead to the recommendations of using the central line for potassium chloride solution with concentrations above 40 mmol/L (Asmar, Mohandas and Wingo 2012; Ballarat Health Services 2014). The administration via a central route has an advantage of thorough dilution by the blood stream and avoidance of extravasation. The physicians in the present study were generally alert that the concentration of potassium chloride solution should be considered when determining the infusion route.

Close patient monitoring is needed due to the high risk involved in intravenous potassium supplementation. Daily serum monitoring is usually recommended for mild and moderate hypokalaemia as patients are not symptomatic and urgent correction is not required (Asmar, Mohandas and Wingo 2012; Northern Sydney Local Health District 2014). Regarding severe levels of hypokalaemia, it is essential to monitor potassium levels as early as possible. Serum potassium monitoring of every 1-2 hours (Kruse *et al.* 1994) or after the administration of 40 mmol potassium (Gloucestershire Hospitals 2014) is generally recommended. However, some literature and guidelines recommended every 2 h–4 h (Asmar, Mohandas and Wingo 2012) or 4 h–6 h (Northern Sydney Local Health District 2014) of serum potassium monitoring. In this study, approximately half of the physicians opted for daily serum potassium monitoring in mild hypokalaemia and every 1 h–2 h in moderate hypokalaemia. When assessing the physicians' preference of serum potassium monitoring in severe hypokalaemia, most of the respondents opted for serum monitoring of every 1 h–2 h. Hence, it can be concluded that the physicians would perform more frequent serum potassium monitoring for more severe hypokalaemia.

In the treatment of hypokalaemia, cardiac monitoring is required in certain conditions. This study revealed that the physicians mostly preferred cardiac monitoring in severe hypokalaemia. However, there were several physicians who stated cardiac monitoring is required in moderate hypokalaemia. This is because the patients can be symptomatic at a moderate hypokalaemia level with muscle weaknesses and cardiac abnormalities, and several guidelines states that cardiac monitoring is necessary in moderate and severe hypokalaemia (Irish Medication Safety Network 2013; Sterns 2021). Patients undergo fast

infusion rate of potassium supplementation is another reason for cardiac monitoring as stated by the physicians in this study. Cardiac monitoring is recommended in fast correction or infusion above 20 mmol/h of potassium, as rapid administration can cause potassium toxicity (Irish Medication Safety Network 2013; Northern Sydney Local Health District 2014). In hyperkalaemia, major ECG changes can occur, leading to cardiac arrhythmias and cardiac arrest without apparent warning. However, the rate of potassium infusion for cardiac monitoring to be initiated may vary with the rates as low as 10 mmol/h of potassium has been recommended for cardiac monitoring (Ballarat Health Services 2014; Irish Medication Safety Network 2013; Northern Sydney Local Health District 2014). However, physicians in this study mostly opted choices of rates above 10 mmol/h and 20 mmol/h, respectively, for cardiac monitoring. The physicians also chose to perform cardiac monitoring in patients who received high concentrated potassium solutions which include concentrations above 80 mmol/L due to the risk of potassium toxicity. Indeed, the recommendations from available guidelines and literature for cardiac monitoring are vary between 60 mmol/L and 80 mmol/L (Irish Medication Safety Network 2013; Northern Sydney Local Health District 2014; Royal North Shore & Ryde Hospital 2006), which is reflected in the choices by the respondents in this survey.

One of the objectives of this study was to obtain physician's opinion on the use of premixed potassium chloride formulation. The premixed injection formulation of potassium chloride injection is a diluted form of potassium chloride solution which available in various types of diluents, strengths and volume. Premixed form of injectable are formulated mainly to eliminate the need of reconstitution and ease its administration to the patient (Beany 2010; McDowell *et al.* 2009; Pedersen, Schneider and Scheckelhoff 2009). In the present study, most of the physicians agreed that the premixed formulation is easier to administer to the patient. This finding was in accordance with other international surveys on the use of premixes whereby efficiency was reported as the main factor in using these formulation (Fanikos *et al.* 2007).

The concentrated form of potassium chloride has been associated with serious medical errors and fatality. It is considered as an error prone-medication in dispensing and administration stage. The errors included inadvertent selection, wrongly given as bolus or rapid administration and wrongly used as a diluent (Reeve, Allinson and Stevens 2005; Wetherton *et al.* 2003). A systemic review revealed that the reconstitution and administration of drug in intravenous therapy had the highest error probability (McDowell *et al.* 2009). Error rates of 21% have been reported during the preparation of intravenous admixtures (Fanikos *et al.* 2007). A previous study which observed intravenous drug preparation and administration revealed 265 errors out of 483 drug preparations and 447 drug administrations (Taxis and Barber 2003). A prospective audit by Cousins and colleagues on intravenous preparation and administration showed uncontrolled risks and commented that intravenous therapy should be considered as a high-risk activity. With these grave concerns, efforts have included the elimination of drug reconstitution before administration. This can be achieved by using premixes or ready-to-use formulations (Schlom and May 2006). By using premixes, the accuracy of preparation improved and error rates has also been shown to decrease to 0.3% (Fanikos *et al.* 2007). Premixes allows the elimination of the reconstitution step in intravenous admixture preparation, thus reducing the number of steps involved which can reduce the probability of error (McDowell *et al.* 2009). Additionally, other premixed products have been associated with fewer errors with less than 1% error rate compared to 9% in IV mixtures requiring compounding (Ruble 2008). In the present study, slightly than half of the physicians also agreed that the premixed formulation is safer for the patients.

Although premixes are associated with better efficiency in workflow of drug preparation and administration, there were several disadvantages noted. One of the

arguments against using premixes was that having a premixed formulation may make dosing less flexible (McDowell *et al.* 2009). In this study, the choice of 'premixed formulation has limited choice of concentration' was opted by 42.0% of physicians. Besides, with more strengths of premixed formulations available, selection error could occur (McDowell *et al.* 2009). One of the physician in this study raised the concern that having many strengths could be confusing to the prescriber. However, whether an individualised dosing is needed in intravenous potassium replacement therapy has never been studied. Indeed, individualised doses in intravenous therapy have been shown to increase wastage (Ruble 2008). Meanwhile, cost and storage constraints were another concerns on the used of premixed formulation. More storage space is probably needed as a ready-to-use medication is usually bulkier. Also, the availability of different strengths would mean more items to be stored. Nevertheless, there are suggested potential benefits in inventory management from the use of premixes (Ruble 2008). A reduction in the use of diluents and other compounding materials such as syringes and needles can be achieved. Costs associated with staff hours needed for compounding and medicine wastage may also be reduced by the use of premixes (Bates *et al*. 2000; Ruble 2008).

Using premixed formulations are not without any risks. Fluid overload from intravenous fluid therapy is a problem especially in frail and elderly patients due to the reduced ability to excrete excess water (Rolls and Phillips 1990). Intravenous fluid therapy has also been associated with drug-induced deaths in medical inpatients (Porter and Jick 1977). The premixed formulation of potassium chloride literature states to use with caution in patients at risk of fluid retention and edema (Baxter Healthcare Corporation 2005). The infusion of this premix might cause fluid overload which can result in the dilution of serum electrolytes. In this survey, 33.3% of physicians chose the option 'the premixed formulation is not suitable for patients with fluid overload risks'. This finding reflects that the physicians were aware of the cautious that should be take when using premixed formulation.

## STUDY LIMITATIONS

The responding physicians of this survey had a median age of 35.5 years old and majority were below 40 years old. Most of the physicians had working experiences of 15 years and below. Therefore, there was a potential of non-response bias as there were lack of responses from more senior physicians.

## CONCLUSION

This study revealed that there were variations in the prescribing practices among the responding physicians for the treatment of hypokalaemia in adult patients. This finding suggested the lack of standard in intravenous potassium chloride supplementation in the treatment of hypokalaemia and supported the need to have a standardised guideline to improve the safety of intravenous potassium supplementation. Majority of physicians were in favour of premixed formulation for easy administration and patient safety. However, further prospective studies on the feasibility of premixed formulations is warranted.

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