Original Article

Drug Utilization Review of Potassium Chloride Injection Formulations Available in a Private Hospital in Kuching, Sarawak, Malaysia

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Abstract

Background: **The concentrated potassium chloride injection is a high-alert medication and replacing it with a pre-mixed formulation can reduce the risks associated with its use. The aim of this study was to determine the clinical characteristics of patients receiving different potassium chloride formulations available at a private institution. The study also assessed the effectiveness and safety of pre-mixed formulations in the correction of hypokalaemia.**

Methods: **This was a retrospective observational study consisting of 296 cases using concentrated and pre-mixed potassium chloride injections in 2011 in a private hospital in Kuching, Sarawak, Malaysia.**

Results: **There were 135 (45.6%) cases that received concentrated potassium chloride, and 161 (54.4%) cases that received pre-mixed formulations. The patients' clinical characteristics that were significantly related to the utilization of the different formulations were diagnosis ($P < 0.001$), potassium serum blood concentration ($P < 0.05$), and fluid overload risk ($P < 0.05$). The difference observed for the cases that achieved or maintained normokalaemia was statistically insignificant ($P = 0.172$). Infusion-related adverse effects were seen more in pre-mixes compared to concentrated formulations (6.8% versus 2.2%, $P < 0.05$).**

Conclusion: **This study provides insight into the utilization of potassium chloride injections at this specific institution. The results support current recommendations to use pre-mixed formulations whenever possible.**

Keywords: *potassium chloride, electrolytes, hypokalaemia, drug utilization evaluation, drug-use review*

Introduction

Concentrated potassium chloride injections are high-alert medications with the potential to cause grievous harm when misused. Hyperkalaemia, which can lead to ventricular fibrillation, is the main risk with the use of intravenous potassium chloride (1–3). Rimmer JM et al., reported that 58% of hyperkalaemia episodes were due to potassium chloride intravenous supplementation and are more common in the elderly and patients with renal insufficiency (2). The manufacturer also advises that potassium chloride injections should be used with great care in renal impairment due to potential potassium retention (4). In addition to hyperkalaemia, concentrated potassium chloride injections are also associated with medical errors, with even fatalities being reported (5–8). Errors identified include incorrect identification of product and incorrect preparation or dilution (9,10). Therefore, risk-reduction strategies have included the implementation of guidelines for the administration of concentrated potassium chloride injections, separation of storage areas, applying high-alert labelling, removal from patient care areas, and the use of pre-mixed formulations (11,12).

In this private hospital, these steps have been implemented in the interest of patient safety. The use of pre-mixed formulation was introduced in 2010, which were specially imported as it was not registered in Malaysia. This study was conducted to gain insight into the utilization of the different potassium chloride injections available at this institution and to assess the effectiveness and

safety of the new pre-mixed potassium chloride injection formulations.

Materials and Methods

This study was conducted in a private hospital in Kuching, Sarawak, Malaysia, and retrospectively reviewed the utilization of different potassium chloride injections in 2011. All cases using potassium chloride injections were selected for this study, with the exception of those involving patients below the age of 18. The formulations of potassium chloride injections that were evaluated were either a concentrated form that consisted of (1) potassium chloride concentrate (1 g, 13.4 mmol) in a 10 mL injection or a pre-mixed formulation that consisted of (2) 20 mEq of potassium chloride in a 0.9% sodium chloride injection (1 L), (3) 40 mEq of potassium chloride in a 0.9% sodium chloride injection (1 L), or (4) 20 mEq potassium chloride in a 5% dextrose injection (1 L). These formulations were administered according to the institution's policy for potassium chloride injections, which states that pre-mixes should be used whenever possible and that if concentrated potassium chloride is used, it should be ideally diluted with 0.9% sodium chloride (unpublished work). The stated infusion rates are 1 mEq/kg/h or less than 40 mEq/h.

A self-designed form was used to collect data. Data that were retrieved from patient's medical records included demographic data; clinical characteristics, such as main diagnoses and concurrent medical problems; type of potassium chloride injection used; and concurrent medications. Effectiveness was defined as achieving or maintaining normakalaemia with or without reversal of hypokalaemic symptoms. To assess effectiveness, serum potassium levels before and after potassium chloride injection administration, and time to reach normokalaemia after potassium chloride injection administration were recorded. Time to reach normokalaemia was recorded as less than 12 h, between 12 to 24 h, and more than 24 h after potassium chloride injection administration. To assess safety, the presence of adverse effects from the potassium chloride administration was noted. Adverse effects included symptoms listed in the literature and product leaflet, which were presence of hyperkalaemia, fluid overload symptoms (e.g. edema), and infusion-related adverse effects such as pain or phlebitis at infusion site, febrile response, and extravasation (1,13,14).

Statistical analysis was performed by using the Statistical Package for the Social Sciences Version (SPSS) 15.1. Demographic data were analysed descriptively, and results were presented in mean or frequency (percentage). A chi-square test was performed to determine whether there was a relationship between the clinical characteristics of the patients receiving different potassium chloride injections. Fisher's exact test was performed to evaluate the differences of effectiveness among different potassium chloride injections as more than 20% of cells have an expected frequency of less than five. For the evaluation of its safety, a chi-square test or Fisher's exact test was performed to evaluate the differences of hyperkalaemia, fluid overload symptoms, and the frequency of infusion-related adverse effects among the concentrated and pre-mixed formulations. The statistically significant level was set at a *P* value of 5%.

Results

Out of the 296 cases in this study, 135 (45.6%) received concentrated potassium chloride and 161 (54.4%) received one of the pre-mixed formulations.

Demographic Data

The distribution of patients with regards to age and gender is presented in Table 1. The mean age for patients in this study was 58 years old, with a range of 19 to 95 years old. Gender distribution was similar in the concentrated potassium chloride injection group and the 20 mEq potassium chloride in 0.9% sodium chloride injection group.

Clinical Characteristics

A chi-square test revealed that the type of injection used was related to the patient's diagnosis ($P < 0.001$). Table 2 lists the top five main diagnoses for the patients who received the concentrated or pre-mixed formulations. For patients diagnosed with stroke, cancer, and gastrointestinal disorders, pre-mixed formulations were mainly used (61.1%, 66.7%, and 62.9%, respectively). For patients diagnosed with sepsis and those undergoing invasive procedures, the concentrated formulation was mainly used (68.0% and 95.8%, respectively).

The use of the concentrated and pre-mixed formulations was related to the presence of fluid overload risks ($P = 0.008$) (Table 3), such as congestive heart failure, renal impairment, and edema. In the presence of these risks, the concentrated form was mostly used compared to

a pre-mixed formulation (60% versus 40%).

The differences in the type of injection used in relation to different serum potassium levels before the potassium chloride injection were statistically significant (P = 0.013) (Table 4). For cases that received the concentrated injection, the majority had mild hypokalaemia levels (42.4%), while the majority of cases that received the pre-mixed formulations were normokalaemic (40.1%).

Table 1: Demographic characteristics of patients

Characteristics	Formulation [a]			
	A	B	C	D
Number of cases, no. (%)	135 (45.6)	133 (44.9)	5 (1.7)	23 (7.8)
Age, mean years ± SD	61.02 (SD 17.5)	53.80 (SD 15.98)	44.25 (SD 24.05)	60.90 (SD 9.57)
Age range (years), no. (%)				
18–29	9 (6.7)	11 (8.3)	3 (60.0)	0 (0.0)
30–49	24 (17.9)	40 (30.3)	0 (0.0)	3 (13.0)
50–64	44 (32.8)	42 (31.8)	1 (20.0)	11 (47.8)
65 and above	57 (42.5)	39 (29.5)	1 (20.0)	9 (39.1)
Gender, no. (%)				
Male	66 (49.3)	62 (47.0)	0 (0.0)	7 (30.4)
Female	68 (50.7)	70 (53.0)	3 (100.0)	16 (69.6)

[a] A: potassium chloride concentrate 1 g (13.4 mmol) in 10 mL injection, [a] B: 20 mEq potassium chloride in 0.9% sodium chloride injection 1 L, [a] C: 40 mEq potassium chloride in 0.9% sodium chloride injection 1 L, [a] D: 20 mEq potassium chloride in 5% dextrose injection 1 L.

Table 2: Proportion of top five main diagnosis in concentrated and pre-mixed group

Top Five Main Diagnosis (%)	Type of Injection [a]	
	Concentrated (%)	Pre-mixed (%)
Stroke (18.2)	38.9	61.1
Cancer (18.2)	33.3	66.7
Gastrointestinal disorders (11.8)	37.1	62.9
Sepsis (8.4)	68.0	32.0
Invasive Procedures (8.1)	95.8	4.2

Chi-square test (n = 296): P < 0.001.

[a] Concentrated group consist of potassium chloride concentrate 1 g (13.4 mmol) in 10 mL injection. Pre-mixed group consist of 20 mEq potassium chloride in 0.9% sodium chloride injection 1 L, 40 mEq potassium chloride in 0.9% sodium chloride injection 1 L and 20 mEq potassium chloride in 5% dextrose injection 1 L.

Table 3: Frequency of cases present with fluid overload risks among concentrated and pre-mixed formulations

Presence of Fluid Overload Risks	Type of Injection [a]		Pearson's Chi-Square Test (n = 296)
	Concentrated, n (%)	Pre-mixed, n (%)	
Present	39 (60)	26 (40)	P = 0.008 [b]
Not Present	96 (41.6)	135 (58.4)	

[a] Concentrated group consist of potassium chloride concentrate 1 g (13.4 mmol) in 10mL injection. Pre-mixed group consist of 20 mEq potassium chloride in 0.9% sodium chloride injection 1 L, 40 mEq potassium chloride in 0.9% sodium chloride injection 1 L and 20 mEq potassium chloride in 5% dextrose injection 1 L. [b] P < 0.05.

Effectiveness

To measure the effectiveness of the different potassium chloride injections, the frequency of cases achieving or maintaining normokalaemia were observed (Table 5). The number of cases achieving or maintaining normokalaemia was similar among those who received the concentrated formulation and those who received the pre-mixed formulation; no statistical difference was observed (P = 0.172). Most cases that received the concentrated formulation achieved normokalaemia between 12 to 24 h, while those who received the pre-mixed formulations took longer. However, the difference among the different formulations was also not statistically significant (P = 0.518).

Safety

Hyperkalaemia were seen more in those who received the concentrated injection compared to pre-mixed formulations (Table 6). However, the difference of the frequency of hyperkalaemia in those who received the concentrated and pre-mixed formulations was not statistically significant (P = 0.065). Conditions associated with potassium retention properties, such as renal impairment, dehydration, and diabetes mellitus, were related to the frequency of hyperkalaemia (P = 0.007) (Table 7). The concurrent use of other medication with potassium retention properties in the cases with hyperkalaemia was not statistically significant (P = 0.314). There were also some cases with normokalaemic levels

Table 4: Distribution of serum potassium levels before potassium chloride injection administration among cases using concentrated and pre-mixed formulations

Serum Potassium Levels Before Potassium Chloride Administration	Type of Injection [a]		Pearson's Chi-Square Test
	Concentrated, *n* (%)	Pre-mixed, *n* (%)	
Mild Hypokalaemia (3.0–3.5 mmol/L)	50 (42.4%)	42 (28.6%)	P = 0.013 (n = 265) [b]
Moderate Hypokalaemia (2.5–2.9 mmol/L)	34 (28.8%)	36 (24.5%)	
Severe Hypokalaemia (below 2.5 mmol/L)	8 (6.8%)	10 (6.8%)	
Normokalaemia (3.6–5.0 mmol/L)	26 (22.0%)	59 (40.1%)	

[a] Concentrated group consist of potassium chloride concentrate 1 g (13.4mmol) in 10mL injection. Pre-mixed group consist of 20 mEq potassium chloride in 0.9% sodium chloride injection 1 L, 40 mEq potassium chloride in 0.9% sodium chloride injection 1 L and 20 mEq potassium chloride in 5% dextrose injection 1 L. [b] Among the 296 cases using potassium chloride injections, 265 cases had records of serum potassium levels before potassium chloride injection administration.

Table 5: Effectiveness of different potassium chloride injection formulations

		Formulation [a]				Fisher's exact test
		A	B	C	D	
Number of cases with normokalaemia achieved or maintained among different formulations	Normokalaemia achieved	60	49	3	9	P = 0.172 (n = 181) [b]
	Normokalaemia not achieved	30	20	0	10	
Number of different times to reach normokalaemia or reversal of hypokalaemia symptoms among different formulations	Below 12 h	12	2	0	1	P = 0.518 (n = 76) [c]
	Between 12–24 h	20	8	0	2	
	More than 24 h	16	9	1	5	

[a] A: potassium chloride concentrate 1 g (13.4 mmol) in 10mL injection, B: 20 mEq potassium chloride in 0.9% sodium chloride injection 1 L, C: 40 mEq potassium chloride in 0.9% sodium chloride injection 1 L, D: 20 mEq potassium chloride in 5% dextrose injection 1 L. [b] Among the 296 cases using potassium chloride injections, 181 cases had records for serum potassium levels after potassium chloride injection administration. [c] Among the 296 cases using potassium chloride injections, 76 cases had records for time to reach eukalaemia or reversal of hypokalaemia symptoms.

before administration of the potassium chloride injection. Due to the nature of this study, it was not possible to determine the reason for this situation, but it is possible that the potassium chloride injection was administered for prophylactic purposes. The frequency of hyperkalaemia in these normokalaemic cases was 12%, but this was not statistically significant (P = 0.594) (Table 8).

The frequency of fluid overload symptoms was 1.5% in the concentrated group and 1.9% in the pre-mixed group, and the difference between the two groups were statistically insignificant (P = 0.166) (Table 6). The age range of patients presenting with these symptoms were between 50 to 64 years (n = 3) and 65 years and above (n = 2). Only one case had a risk for fluid overload symptoms, and this was due to renal impairment.

The difference in the number of infusion-related adverse effects (such as pain at infusion site, phlebitis, and febrile response) between the two formulations was statistically significant (P = 0.024) with more seen in the pre-mixed group (Table 6). Age was related to the presence of infusion-related adverse effects (P = 0.05); this was most common in the 30–45 age group.

Table 6: Frequency of adverse effects from potassium chloride administration among concentrated and pre-mixed formulation

Adverse Effect	Type of Injection [a]		
	Concentrated	Pre-mixed	
Presence of hyperkalaemia after potassium chloride injection administration	n = 90	n = 91	Pearson's Chi-Square Test: P = 0.065 (n = 181) [b]
Total	15 (16.7%)	7 (7.7%)	
Fluid Overload Symptoms			
Pulmonary edema	0	2	Fisher's exact test: P = 0.166 (n = 296)
Peripheral edema	2	0	
Other edema	0	1	
Total	2 (1.5%)	3 (1.9%)	
Infusion related adverse effects			
Pain at infusion site	1	2	Fisher's exact test: P = 0.024 (n = 296)
Phlebitis at infusion site	1	8	
Febrile Response	1	1	
Total	3 (2.2%)	11 (6.8%)	

[a] Concentrated group consist of potassium chloride concentrate 1 g (13.4 mmol) in 10 mL injection. Pre-mixed group consist of 20 mEq potassium chloride in 0.9% sodium chloride injection 1 L, 40 mEq potassium chloride in 0.9% sodium chloride injection 1 L and 20 mEq potassium chloride in 5% dextrose injection 1 L. [b] Among the 296 cases using potassium chloride injections, 181 cases had records for serum potassium levels after potassium chloride injection administration.

Table 7: Conditions associated with potassium retention in hyperkalaemia cases

	Number of cases (N = 296) [a]	Frequency of hyperkalaemia cases, n (%)
Conditions associated with potassium retention (renal impairment, dehydration, diabetes mellitus)	181	15 (8.3) [b]
Concurrent medication with potassium retention properties (ACE inhibitors, ARBs, potassium sparing diuretics, NSAIDs)	177	4 (2.2) [c]

[a] Total number of cases using potassium chloride injections. [b] Chi-square test: P = 0.007. [c] Chi-square test: P = 0.314. ACE (angiotensin converting enzyme); ARB (angiotensin receptor blocker); NSAID (non-steroidal anti-inflammatory agent).

Discussion

From this retrospective observation, the use of potassium chloride injections in either a concentrated and pre-mixed formulation was found to be similar. These results differ from another observational study on intravenous potassium chloride prescribing and administration practices in Victoria, Australia, where more than 80% of prescriptions for potassium chloride injections were dispensed with pre-mixed formulations (15). This difference may be because the Australian Council for Safety and Quality in Health Care recommends the removal of concentrated potassium chloride ampoules in patient care areas and replacing them with pre-mixed infusions. Another reason may be due to the fact that in Malaysia, the pre-mixed formulations were not readily available at the time of this study, and the private institution was forced to import it independently.

Currently there is no general consensus regarding the use of particular potassium chloride formulations according to patients' clinical characteristics. However, the product information leaflet for the pre-mixed formulation states that it is to be used with great care in patients with congestive heart failure, severe renal insufficiency, and the presence of edema (4,16). In this study, main diagnoses in the pre-mixed formulations group were mainly cancer, stroke, and gastrointestinal disorders. For patients diagnosed with sepsis and those undergoing invasive procedures, the concentrated formulation was mainly used. However, this study did not examine the differences of the ward settings of these patients. The decision to use the concentrated injection for patients with sepsis or who were undergoing an invasive procedure may be due to the fact that fluid overload is a complication of these conditions (17). It was also found that the concentrated form was mostly used when a risk of fluid overload was present, such as congestive heart failure, renal impairment, and edema. Another observation was that these potassium chloride injections were used even for patients with normokalaemic levels. A potassium chloride injection is not indicated for prophylaxis, although it is common practice that intravenous (IV) administration is used in mild to moderate hypokalaemia cases (18). It is known that there are those at particular risk of hypokalaemia, such as the elderly with chronic diseases and those undergoing surgery. Therefore, this practice may be a reflection of the concern of adverse outcomes in those with risk of hypokalaemia. More study is needed on the use of potassium chloride injections as a prophylaxis of hypokalaemia or in normokalaemic states.

As there are no available published data on the effectiveness of pre-mixed potassium chloride injections, one of the objective of this study was to evaluate the effectiveness of this diluted formulation in the treatment of hypokalaemia or for maintaining normokalaemic levels. However, as this study was an uncontrolled observational study, making general statements regarding the effectiveness and safety of a certain practice may not be convincing. Therefore, the effectiveness and safety of pre-mixed potassium chloride injections in this study can only be compared to the concentrated form. Results suggest that the pre-mixed formulations are as effective as the concentrated form in

Table 8: Frequency of hyperkalaemia cases after potassium chloride injection administration among different serum potassium levels before potassium chloride injection administration

Serum Potassium Levels Before Potassium Chloride Injection Administration	Frequency of Hyperkalaemia Cases After Potassium Chloride Injection Administration	Fisher's exact test (n = 176) [a]
Mild hypokalaemia (3.0–3.5 mmol/L)	4 (6.7%)	P = 0.594
Moderate hypokalaemia (2.5–2.9 mmol/L)	7 (13.5%)	
Severe hypokalaemia (below 2.5 mmol/L)	2 (14.3%)	
Normokalaemia (3.6–5.0mmol/L)	6 (12.0%)	

[a] Among the 296 cases using potassium chloride injections, 176 cases had records for serum potassium levels before and after potassium chloride injection administration.

the treatment of hypokalaemia or for the maintenance of normokalaemia levels, as no statistical differences were observed. This supports the recommendation of using pre-mixed formulations whenever possible (6,15,19,20). It offers a practical alternative to mixing solutions in patient care areas (7). In addition, other pre-mixed products have been associated with fewer mistakes, with an error rate of less than 1% compared to an error rate of 9% in IV mixtures requiring compounding (12,20).

The main concern with administrating potassium through an IV is hyperkalaemia, which can lead to ventricular fibrillation (1–3). Rimmer JM et al. reported that 58% of hyperkalaemia episodes are due to potassium chloride intravenous supplementation. This study found that the frequency of hyperkalaemia was lower in the pre-mixed formulation group but that its difference from the concentrated group was not statistically significant ($P > 0.05$). Thus, the results suggest that when using pre-mixed potassium chloride formulations in the treatment of hypokalaemia or for maintaining normokalaemia, the frequency of hyperkalaemia should not be different from the use of the concentrated form. Among the hyperkalaemia cases in this study, conditions with potassium-retention properties that were present included renal impairment, dehydration, and diabetes mellitus. Rimmer JM et al., also reported that renal dysfunction was the most common predisposing disease state in hyperkalaemia. Other disease states identified were glucose intolerance and metabolic acidosis. However, a study on the rapid correction of hypokalaemia with concentrated potassium chloride revealed no clear relationship between the differences of pre-/post-infusions and serum creatinine levels. Also, none of the subjects with renal impairment developed hyperkalaemia. The investigators advise extreme caution, but rigid recommendations should be avoided as they are not universally applicable (21).

The use of pre-mixed formulations does not come without risk. Fluid overload from IV fluid therapy is one problem, especially in frail and elderly patients due to their reduced ability to excrete excess water (22,23). Cases of fluid overload, such as pulmonary edema and peripheral edema, from IV fluid administration have been reported, even leading to death in rare cases (24,25). In this study, the frequency of fluid overload symptoms in the both concentrated and pre-mixed groups was low, but it still occurred, even in the absence of fluid overload risks. Currently, there are no available reports regarding fluid overload from the use of pre-mixed potassium chloride formulations. However, the prescriber should always keep in mind the risk of fluid overload when using pre-mixed formulations, especially in the elderly.

Other possible adverse effects are infusion related, such as pain and phlebitis at the infusion site, febrile response, and extravasation (4,16,26). Documented incidences of infusion-related phlebitis are between 25% to 35% (27,28). In this study, the frequency of infusion-related adverse effects was significantly more in the pre-mixed group. The 30–45 age group had the most infusion-related adverse effects. This result differs from other studies that have identified old age as one of the risk factors (27,29,30). The only study that seems to support this age group was a study on infusion-related adverse effects seen in vancomycin, where an age below 40 years was a significant risk factor (31).

Conclusion

The results of this exploratory and descriptive study provide insights into the utilization of pre-mixed and concentrated solutions of potassium chloride in a specific private hospital. No statistical differences were observed between the concentrated and pre-mixed formulations groups for achieving normokalaemia. This suggests that the pre-mixed formulations are as effective as the concentrated form in achieving normokalaemia. Nevertheless, it should be noted that this was based on routine clinical data. Despite the limitations of the study, these observations support other recommendations to use pre-mixed formulations whenever possible as the concentrated potassium chloride injection is associated with serious medication errors and is categorized as a high-alert drug. The institution pharmacists can play a role in promoting the use of pre-mixed formulations whenever applicable. However, as the pre-mixed formulations are not currently registered in Malaysia, this causes a barrier in obtaining stock for this particular institution.

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Conflict of Interest

None.

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Authors' Contributions

Conception and design: MHM, SA
Analysis and interpretation of the data, drafting of the article, and collection and assembly of data: MHM
Critical revision of the article for the important intellectual content and final approval of the article: SA

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