ORIGINAL ARTICLE

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

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ABSTRACT

Introduction: The use of concentrated potassium chloride formulation in the intravenous potassium supplementation of hypokalemia treatment is associated with risks of hyperkalemia. This study aimed to assess the safety and effectiveness of a developed guideline on potassium chloride intravenous supplementation with the emphasis on using premixed formulations. The cost implications of using the premixed formulations were compared with the diluted concentrated formulation as well. **Methods:** This was a prospective interventional study conducted in Normah Medical Specialist Centre, Malaysia. A guideline on potassium chloride intravenous supplementation with the emphasis on using premixed formulation was developed and implemented in the treatment of hypokalemia. The safety, effectiveness and cost of using diluted concentrated potassium chloride formulation before the guideline implementation was compared with premixed formulation during the guideline implementation. **Results:** A total of 154 hypokalemia patients in the pre-guideline phase was compared with 28 patients in the guideline implementation phase. None of the patients experienced hyperkalaemia during guideline implementation phase as compared to pre-guideline phase (0.0% versus 3.2%), but the different was not significant (p = 1.000). The proportion of hypokalemia patients with successful corrected potassium levels during guideline implementation phase were not differed significantly from pre-guideline phase (71.4% versus 59.1%, p = 0.218). The used of premixed formulations led to an overall cost reduction due to reduced labour costs as compared to concentrated formulations which was seen in both cases of mild hypokalaemia and moderate to severe hypokalaemia. This labour cost reduction was contributed by a lower total infusion time and elimination of drug preparation time during guideline implementation phase where premixed formulations were solely used. The mean total cost per case of intravenous potassium supplementation in mild hypokalaemia was reduced from RM 376.19 in pre-guideline phase to RM 263.19 during guideline implementation phase. Meanwhile, the moderate to severe hypokalaemia cases showed similar trend whereby the mean total cost per case was reduced from RM 304.17 in pre-guideline phase to RM 207.29 during guideline implementation phase. **Conclusion:** The developed guideline with the emphasis of premixed formulations is safe and effective with impact of cost savings.

Keywords: Potassium chloride injection; Hypokalemia; Intravenous potassium replacement guideline; Premixed formulation

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INTRODUCTION

The used of concentrated potassium chloride formulation in the potassium supplement of hypokalaemia treatment is associated with risks of hyperkalaemia and medication errors (1–3). In order to mitigate these risks, implementing guidelines on the use of premixed potassium chloride formulation to replace the concentrated formulation have been recommended (4). Several institutions have implemented local guidelines on potassium intravenous supplementation (5–7). 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 (8,9). Nevertheless, there is no standard national guideline for the potassium chloride supplementation in Malaysia. It is unknown whether the hospitals in Malaysia have their local guidelines on intravenous potassium supplementation for hypokalaemia, though dilution protocols for potassium chloride may exist (10).

Despite the available of recommendations and guidelines on intravenous potassium supplementation,

variations exist between the dose, concentration, infusion rate, duration, route of potassium chloride injection and the rate of potassium level correction in hypokalaemia treatment (11–14). Most importantly, there is no guideline on the treatment of hypokalaemia by any major medical association (15). Additionally, a search in the Cochrane Database of Systemic Reviews with keywords of 'hypokalaemia', 'potassium disorders' and 'electrolyte disorders' revealed only one systematic review on hyperkalaemia management (16). Besides, only a few of randomized controlled studies on hypokalaemia management are available (17). Several hospitals have performed assessment on their local protocols, and it has shown to be safe and effective. Nevertheless, the measurements of safety and effectiveness are differed among the hospital protocols. Besides, the assessments were involved small sample sizes, were retrospective in nature and had non-homogenous patient populations (18–20).

International standards recommend the incorporation of premixed or ready-to-use formulations in intravenous potassium supplementation guidelines to reduce the risk of medication errors associated with concentrated potassium chloride injections (1,4). This is because the error rates of premixes formulation were suggested to be lower than compounded intravenous medications (21). Errors associated with concentrated potassium chloride injection included incorrect identification of the product, incorrect reconstitution and unintentional bolus administration (22). Premixed formulations can mitigate these risks by eliminating the need to reconstitute and prevent unintentional bolus administration (4,23). A previous study reported a significant reduction of potassium chloride injection-related incidents after introducing premixed formulations along with other safety systems in their haematology ward (24). Additionally, premixed drugs such as premixed dobutamine and premixed immunoglobulin have been found to have comparable effectiveness and safety profile with the concentrated formulations (25,26). Besides, small scale studies have been carried out to evaluate the cost implications of the use of various premixes in hospitals (25,26). The results showed that premixes were able to reduce waste, material costs and staffing needs (21,25,26).

Considering the risks associated with intravenous potassium supplementation and the variations existing in available guidelines, the Normah Medical Specialist Centre, Malaysia has developed a local guideline to assist physicians in treating hypokalaemia. This study aimed to assess the safety and effectiveness of the guideline implementation. The primary objective of the study was to assess the safety of the guideline by comparing the proportion of patients with hyperkalaemia before and during guideline implementation. The secondary objective was to assess the effectiveness of the guideline by comparing the proportion of hypokalaemia patients with corrected serum potassium levels before and during guideline implementation. Besides, the direct costs of using premixed potassium chloride formulations were compared with concentrated formulations in the treatment of hypokalaemia.

MATERIALS AND METHODS

Guideline development and implementation

This was a prospective, interventional study conducted in a 130-bed private hospital (Normah Medical Specialist Centre, Malaysia). It was a quality improvement initiative in the interest of reducing the risks associated with intravenous potassium supplementation. The study was conducted in two phases: pre-guideline implementation and guideline implementation. The safety, effectiveness and cost implications of the developed guideline was compared between the two phases. Safety of potassium chloride intravenous supplementation was defined as proportion of cases with presence of hyperkalaemia. Effectiveness of potassium chloride intravenous supplementation was defined as proportion of cases which achieve normokalaemia. Meanwhile, the direct costs of intravenous potassium chloride supplementation of each case were observed in this study which is the summing up of nursing labour costs and material costs.

The guideline was developed through a literature review of intravenous potassium chloride supplementation for the treatment of hypokalaemia. Besides, safety and effectiveness data from the pre-guideline phase which included intravenous potassium supplementation using concentrated formulation was served as the input for the guideline development. Additional input was obtained from the institution's consultant nephrologist. The guideline outlined the dose and rate of infusion of intravenous potassium supplementation as well as required monitoring according to different levels of hypokalaemia. Maximum concentration, maximum rate of infusion, choice of diluent and route of infusion was recommended in the guideline as well. Additionally, available premixed formulations that can be prescribed at different levels of hypokalaemia were included. The guideline was brought to the institution's Pharmacy & Therapeutics Committee for approval before implementation. Upon approval, the guideline was implemented in all the wards of the institution. The physicians were informed by the pharmacists on the availability of premixed formulations. The developed guideline is presented in Table I.

Inclusion and exclusion criteria

The inclusion criteria was hypokalaemia adult patients with serum potassium levels below 3.5 mmol/litre. Paediatric patients or patients below 18 years old was excluded from this study.

Table I : Normah Medical Specialist Centre (NMSC) guideline on intravenous potassium chloride supplementation in the treatment of hypokalaemia

Serum Potassium Level	Intravenous Replacement (Dose & Rate of Infusion)	Available Premixed Formulation	Monitoring
Mild Hypokalaemia: **3.0 - 3.4 mmol/L**	10 - 20 mmol over 24 hours	• 10 mmol KCL in 500 ml 0.9% NaCL • 20 mmol KCL in 1000 ml Dextrose Saline	• Daily serum potassium levels monitoring
Moderate Hypokalaemia: **2.5 – 2.9 mmol/L**	10 – 20 mmol over 24 hours *Note: A faster rate of infusion may be needed for symptomatic patients. See further notes below.*	• 10 mmol KCL in 500 ml 0.9% NaCL • 20 mmol KCL in 1000 ml Dextrose Saline • 20 mmol KCL in 100 ml 0.9% NaCL • 40 mmol KCL in 1000 ml 0.9% NaCL	• 12 hourly serum potassium levels monitoring until it is 3.0 mmol/L, then check daily
Severe Hypokalaemia: **Less than 2.5 mmol/L**	20 – 40 mmol over 1 – 2 hours *Repeat as necessary until target level reached*	• 20 mmol KCL in 100 ml 0.9% NaCL	• 1 – 2 hourly serum potassium levels • Cardiac monitoring (continuous ECG monitoring of heart rate and rhythm)
Critical Hypokalaemia: **Less than 2.0 mmol/L**	40 mmol over 1 – 2 hours *Repeat as necessary until target level reached*	• Nil	• 1 – 2 hourly serum levels • Cardiac monitoring (continuous ECG monitoring of heart rate and rhythm)

Notes:

- **Empirical intravenous treatment of hypokalaemia (repeated doses may be necessary)**
- **20 mmol of potassium = 1.5 grams potassium**
- **Maximum Concentration: 200 mmol per litre. Cardiac monitoring is needed** for concentrations above 40 mmol per litre. ***See further notes on Route of Infusion.***
- **Maximum Rate of Infusion: 20 mmol per hour. Cardiac monitoring is needed** for infusion rates above 20 mmol per hour. ***See further notes on Route of Infusion***
- **Diluent:** Sodium chloride solutions are recommended as diluents and **dextrose solutions should be avoided** as these can cause an increase in insulin serum levels which lead to rebound hypokalaemia.
- ***Route of Infusion:*** **For peripheral lines, maximum concentration should be 40 mmol per litre and rate of infusion no faster than 20 mmol per hour.** A large peripheral line is needed for concentrations above 40 mmol per litre. Central line is needed for higher concentrations and faster rates of infusion.
- Extreme caution is needed in **renal impairment patients**.
- Expert advice is needed in the treatment of hypokalaemia in **diabetic ketoacidosis**.

Sample size determination

The sample size was calculated based on the primary objective of the study by using Pocock's Formula for a comparison of two proportions (27). According to a pilot study conducted in the present institution, the proportion of patients without hyperkalaemia after concentrated intravenous potassium chloride was 0.833 (83.3%) while the proportion of patients without hyperkalaemia after premixed intravenous potassium chloride was 0.923 (92.3%) (28). These findings were applied in the sample size calculation and the calculated sample size was 206 patients in each arm.

Data collection

During the pre-guideline implementation phase, data on safety, effectiveness and cost of using concentrated potassium chloride formulation for the treatment of hypokalaemia was collected. A self-designed form, validated by two experts from School of Pharmaceutical Sciences, Universiti Sains Malaysia and consultant nephrologist from Normah Medical Specialist Centre was used to collect data throughout the study. The collected data included demographics, patient's clinical characteristics (e.g., diagnosis, serum potassium levels before and after treatment, and patient's concurrent medications) and details of intravenous potassium supplementation (e.g., empirical dose prescribed, amount of potassium given, number of doses given, changed in serum potassium level, maximum rate of infusion used, concentration and vehicle of final solution). Hypokalaemia levels are categorized by serum potassium levels as mild (3.0-3.4 mmol/litre), moderate (2.5-2.9 mmol/litre) and severe (below 2.5 mmol/litre) (29,30). Hyperkalaemia was defined as serum potassium levels above 5.0 mmol/litre (31).

The direct costs estimated in this study included labour costs and material costs. Labour costs included preparation time and infusion time while material costs included potassium chloride injection and materials used for reconstitution. Labour cost is extrapolated to ringgit Malaysia (RM) by multiplying nursing time

with nursing wage. The nurses who carried out the intravenous potassium preparation filled these details in the self-designed form.

During the guideline implementation period, the principal investigator (first author) and the hospital pharmacists monitored all the intravenous premixed potassium chloride supplementation throughout the hospital and recommendations were made to the physicians according to the guideline. The same data as in the pre-guideline implementation phase of the study was collected on safety, effectiveness and cost of intravenous potassium supplementation.

Data analysis

Statistical Package for the Social Sciences (SPSS) Version 27.0 was used to analyse demographic data, clinical characteristics of patients and details of potassium chloride intravenous supplementation. Considering the data collected to assess safety, effectiveness and costs, categorical variables were compared using Chi-Square test or Fisher's Exact test where appropriate. Meanwhile, the numerical variables were compared using Student t-test if the data is normally distributed while Mann-Whitney U test was used if the data is not normally distributed. Statistical significance was set at a p value of less than 0.05 for all the analysis.

Ethics approval

This study has obtained ethics approval from both Normah Medical Specialist Centre Ethics Committee and the Human Research Ethics Committee (JEPeM), Universiti Sains Malaysia (approval number: USM/JEPeM/19070398).

RESULTS

Clinical characteristics of patients

The pre-guideline implementation phase involved 206 patients who involved the use of diluted concentrated potassium chloride formulation while 43 patients involved the use of premixed formulation during the guideline implementation phase. Only cases which complied with the guideline's recommendation was included in the study during the guideline implementation phase. The mean age of patients was not differed significantly between the two groups with 61.52 years in the pre-guideline implementation group and 56.51 years in the guideline implementation group (Table II).

The primary diagnosis or reason for admission during pre-guideline implementation phase were mainly neurological and cardiac disorders (18%), respiratory disorders (17%) and gastrointestinal disorders (17%) while it was mostly renal disorders and electrolyte imbalances (27.9%) during the implementation phase. The mean serum potassium levels of the patients before potassium supplementation in the pre-implementation phase were significantly lower than during guideline implementation phase (2.9 mmol/L versus 3.1 mmol/L). In the pre-guideline implementation phase, majority of patients had mild and moderate hypokalaemia (49.0% and 37.4% respectively). Meanwhile, the patients recruited during the guideline implementation phase were mainly having mild hypokalaemia (79.1%).

During the treatment of hypokalaemia, majority of the patients in the pre-guideline phase and guideline implementation phase (75.7% and 74.4% respectively) had factors associated with hypokalaemia. These factors include receiving drugs that can cause hypokalaemia (diuretics, insulin, beta 2 agonists, glucocorticoids and penicillin group antibiotics) and conditions that can cause hypokalaemia (gastrointestinal loss, cancer, alkalosis, and malabsorption). The patients in both pre-guideline and guideline implementation groups (59.7% and 58.1% respectively) had also factors associated with potassium retention properties, such as having conditions associated with potassium retention (renal impairment, dehydration, diabetes mellitus and acidosis) and receiving drugs with potassium retention properties (angiotensin receptor blockers, ACE inhibitors, beta blockers, non-steroidal anti-inflammatory drugs and digoxin).

Potassium chloride supplementation

The details of intravenous potassium supplementation are illustrated in Table III. There were significant differences in the empirical dose prescribed, maximum rate of infusion and concentration of final solution used between the pre-guideline and guideline implementation phase. During the pre-guideline implementation, around half (53.4%) of the cases used empirical doses of 20 mmols and below while majority (86.0%) of cases used these doses during the guideline implementation phase. Only 40.8% of the cases in pre-guideline phase used a slow infusion rate while majority (81.4%) used it during the guideline implementation phase. When assessing the concentration of potassium chloride, approximately half (51.9%) of cases during pre-guideline phase used a higher concentration of 40 mmols/litre and above as compared to concentrations of below 40 mmols/litre used among majority of the cases (86.0%) during the guideline implementation phase.

Safety and effectiveness of intravenous potassium supplementation

Only cases which involved the monitoring of serum potassium were included in the assessment of safety and effectiveness of intravenous potassium supplementation (Table IV). Among the 206 hypokalemia cases in the pre-guideline implementation phase, 154 (74.8%) cases were involved in the serum potassium monitoring after the treatment. Whereas, among the 43 cases during the guideline implementation phase, 28 cases (65.1%) were involved serum potassium monitoring after the treatment. Only 5 cases (3.2%) were presented with

Table II : Clinical characteristics of patients

Characteristics	Pre-guideline Implementation Phase (n = 206)	Guideline Implementation Phase (n = 43)
[a]**Age (year); mean ± SD (range)**	61.52 ± 19.66 (19-94)	56.51 ± 19.90 (18-94)
Primary Diagnosis/Reason for Admission, no. (%)		
Neurological and Cardiac Disorders	37 (18.0)	6 (14.0)
Respiratory Disorders	35 (17.0)	8 (18.6)
Gastrointestinal Disorders	35 (17.0)	8 (18.6)
Renal Disorders and Electrolyte Imbalances	32 (15.5)	12 (27.9)
Sepsis / Septic Shock	23 (11.2)	1 (2.3)
Oncology Cases	19 (9.2)	0 (0.0)
Surgical Procedures	16 (7.8)	6 (14.0)
Others	9 (4.4)	2 (4.7)
[b]**Serum Potassium Levels, mean ± SD mmol/L (range)**	2.9 ± 0.4 (1.5-3.4)	3.1 ± 0.2 (2.2-3.4)
Hypokalaemia Levels, no. (%)		
Mild Hypokalaemia (3.0-3.4mmol/L)	101 (49.0)	34 (79.1)
Moderate Hypokalaemia (2.5-2.9mmol/L)	77 (37.4)	8 (18.6)
Severe Hypokalaemia (below 2.5mmol/L)	28 (13.6)	1 (2.3)
[c]**Factors associated with hypokalaemia during treatment, no. (%)**		
Yes:	156 (75.7)	32 (74.4)
On drug-inducing hypokalaemia	114 (55.3)	24 (55.8)
Gastrointestinal loss (diarrhoea and vomiting)	54 (26.2)	10 (23.3)
Conditions that can cause hypokalaemia	49 (23.8)	4 (9.3)
No	50 (24.3)	11 (25.6)
[d]**Factors associated with potassium retention during treatment, no. (%)**		
Yes:	123 (59.7)	25 (58.1)
Conditions associated with potassium retention	109 (52.9)	23 (53.5)
Drugs with potassium retention properties	71 (34.5)	19 (44.2)
No	83 (40.3)	18 (41.9)

Statistical test analysis results:

[a]Mann-Whitney U Test: Z= -1.615, p = 0.106

[b]Mann-Whitney U Test: Z = -3.570, p < 0.001

[c]Chi-Square Test: p = 0.856

[d]Chi-Square Test: p = 0.849

hyperkalaemia during the pre-guideline implementation phase which solely involved the use of concentrated formulations. Whereas, the used of premixed formulation during the guideline implementation phase did not caused any occurrence of hyperkalaemia. Besides, 59.1% of the cases in the pre-guideline implementation phase achieved normokalaemia as compared to 71.4% during the guideline implementation phase.

Significantly more doses of potassium chloride were required to achieve normokalaemia in the pre-guideline implementation phase as compared to the guideline implementation phase (3.3 doses versus 2.2 doses) (p = 0.023). The mean amount of potassium needed to achieve normokalaemia was 73.03 mmols in the pre-guideline implementation phase compared to 49.00 mmols in the guideline implementation phase. The mean changed in serum potassium level was 0.9 mmols/litre in the pre-guideline and 0.7 mmols/litre in the guideline implementation phase. The serum level changed was considered as zero if there was no changed in the patients' serum level or a dropped in serum level was seen.

Cost associated with intravenous potassium supplementation

The direct costs of using different formulations during

Table III : Details of intravenous potassium chloride supplementation

Details	Pre-guideline Implementation Phase (n = 206)	Guideline Implementation Phase (n = 43)	Chi-square test analysis results
Empirical dose:			
20 mmols and below	110 (53.4)	37 (86.0)	p < 0.001
Above 20 mmols	96 (46.6)	6 (14.0)	
Maximum rate of infusion:			
Slow (over 24 hours)	84 (40.8)	35 (81.4)	p < 0.001
Moderate (over 3-16 hours)	66 (32.0)	8 (18.6)	
Fast (over 0.5-2 hours)	56 (27.2)	0 (0.0)	
Concentration of final solution:			
Below 40 mmols/litre	99 (48.1)	37 (86.0)	p < 0.001
40 mmols/litre and above	107 (51.9)	6 (14.0)	
Vehicle of final solution:			
Dextrose diluents	60 (29.1)	7 (16.3)	p = 0.084
Non-dextrose diluents	146 (70.9)	36 (83.7)	

n = number of cases. The number of cases referred to cases which used concentrated potassium chloride injection during pre-guideline implementation phase and cases which used pre-mixed potassium chloride injection during guideline implementation phase.

Table IV : Safety and effectiveness of intravenous potassium supplementation

	Pre-guideline Implementation Phase (n = 154)	Guideline Implementation Phase (n = 28)	p-value	Statistical Test
Safety				
Proportion of cases with presence of hyperkalaemia, n (%)	5 (3.2)	0 (0.0)	p = 1.000 (n =154)	Fisher's Exact Test
Proportion of cases without presence of hyperkalaemia, n (%)	149 (96.8)	28 (100.0)		
Effectiveness				
Proportion of cases which achieved normokalaemia (3.5-5.0 mmol/litre), n (%)	91 (59.1)	20 (71.4)	p = 0.218 (n = 182)	Chi-Square Test
Proportion of cases which did not achieve normokalaemia (3.5-5.0 mmol/litre), n (%)	63 (40.9)	8 (11.3)		
Number of potassium chloride doses needed to achieve normokalaemia, mean±SD; (range)	3.3 ± 2.5; (1-12)	2.2 ± 2.3; (1-11)	Z = -2.268, p = 0.023 (n = 111)	Mann-Whitney U Test
Amount of potassium needed to achieve normokalaemia, mean (mmols) ± SD; (range)	73.03 ± 66.37; (6.67-346.60)	49.00 ± 46.10; (20.00 – 220.00)	Z = -1.473, p = 0.141 (n = 111)	Mann-Whitney U Test
Changes of serum potassium level in cases which achieved normokalaemia, mean (mmol/litre) ± SD	0.9 ± 0.4	0.7 ± 0.4	Z = -1.097, p = 0.273 (n = 111)	Mann-Whitney U Test

n = number of cases. The number of cases referred to cases which used concentrated potassium chloride injection during pre-guideline implementation phase and cases which used premixed potassium chloride injection during guideline implementation phase.

pre-guideline and guideline implementation phase was compared using decision tree analysis (Figure 1 and 2). There were 101 mild hypokalaemia cases analysed during pre-guideline implementation phase and 34 mild hypokalaemia cases during guideline implementation phase. The mean drug preparation time for cases using concentrated formulation was 17.7 minutes (Table V). Cases using premixed formulation did not require preparation as it was a ready-to-use formulation. The mean infusion time using concentrated formulation was

Table V : Costs associated with intravenous potassium chloride supplementation in mild hypokalaemia cases

	Pre-guideline implementation phase with concentrated formulation (n = 101)	Guideline implementation phase with premixed formulation (n = 34)	p-value	Statistical Test
Drug preparation time (minutes); mean ± SD (range)	17.7 ± 16.7 (3.0 – 90.0)	Nil	Not applicable	Not applicable
Total infusion time (hours); mean ±SD (range)	47.3 ± 49.5 (1.0 – 240.0)	31.8 ± 23.1 (8.0 – 120.0)	Z = -1.006 p = 0.314	Mann-Whitney U Test
Total nursing time (hours); mean ± SD (range)	47.6 ± 49.7 (1.1 – 241.0)	31.8 ± 23.1 (8.0 – 120.0)	Z = -2.508 p = 0.012	Mann-Whitney U Test
Total labour cost (RM); mean ± SD (range)	351.85 ± 367.33 (8.01 – 1780.99)	234.74 ± 170.77 (59.12 – 886.80)	Z = -2.508 p = 0.012	Mann-Whitney U Test
Total material cost (RM) mean ± SD (range)	24.35 ± 20.52 (6.06 – 118.84)	28.45 ± 23.89 (4.40 – 107.10)	Z = -0.999 p = 0.318	Mann-Whitney U Test
Total cost of intravenous potassium chloride supplementation, (RM); mean ± SD (range)	376.19 ± 382.02 (14.07 – 1865.39)	263.19 ± 186.87 (63.52 – 955.95)	Z = -0.578 p = 0.563	Mann-Whitney U Test

n = number of cases. The number of cases referred to cases which used concentrated potassium chloride injection during pre-guideline implementation phase and cases which used premixed potassium chloride injection during guideline implementation phase.

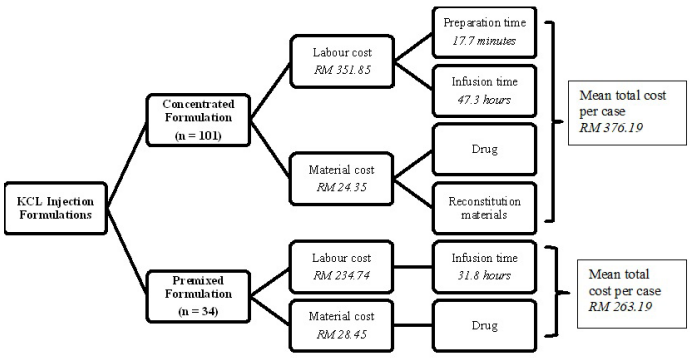

Figure 1 : Decision tree analysis on cost implications of intravenous potassium chloride (KCL) formulations used in mild hypokalemia cases.

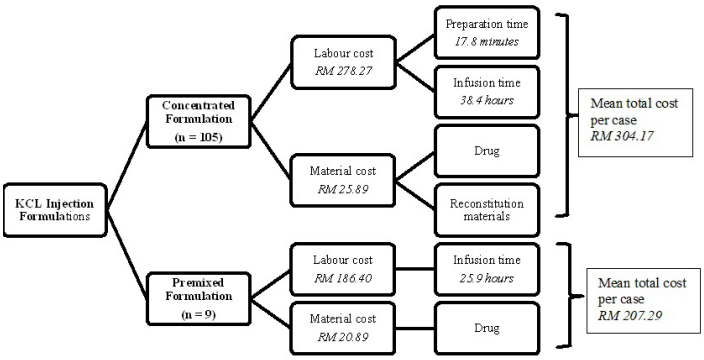

Figure 2 : Decision tree analysis on cost implications of intravenous potassium chloride (KCL) formulations used in moderate to severe hypokalemia cases

longer than premixed formulation (47.3 hours versus 31.8 hours). The mean total nursing time used during pre-guideline implementation phase was significantly more than guideline implementation phase (47.6 hours versus 31.8 hours). This led to a significantly lower mean total labour cost during guideline implementation phase compared to pre-guideline phase (RM 234.74 versus RM 351.85). Despite a higher mean total material cost with premixed formulations used in the guideline implementation phase as compared to concentrated formulation in pre-guideline phase (RM 28.45 versus RM 24.35), the mean total cost per case of intravenous potassium supplementation was lower during guideline implementation phase compared to pre-guideline phase (RM 263.19 versus RM 376.19).

Regarding the moderate to severe hypokalaemia cases, there were 105 cases analysed during pre-guideline implementation phase and 9 cases during guideline implementation phase (Table VI). The mean drug preparation time for cases using concentrated formulation was 17.8 minutes. Besides, the mean infusion time using concentrated formulation was longer than premixed formulation (38.4 hours versus 25.9 hours). The mean total nursing time used during pre-guideline phase was higher than the guideline implementation phase as well (38.6 hours versus 25.9 hours). This led to a higher mean total labour cost during pre-guideline phase compared to guideline implementation phase (RM 278.27 versus RM 186.40). The mean total material cost was lower during guideline implementation phase compared to pre-guideline implementation phase (RM 20.89 versus RM 25.89). Lower mean total cost per case of

Table VI : Costs associated with intravenous potassium chloride supplementation in moderate to severe hypokalaemia cases

	Pre-guideline implementation phase with concentrated formulation (n = 105)	Guideline implementation phase with premixed formulation (n = 9)	p-value	Statistical Test
Drug preparation time (minutes); mean ± SD (range)	17.8 ± 20.5 (3.0 – 160.0)	Nil	Not applicable	Not applicable
Total infusion time (hours); mean ± SD (range)	38.4 ± 48.7 (0.5 – 216.0)	25.9 ± 8.8 (16.0 – 48.0)	Z = -0.497 p = 0.619	Mann-Whitney U Test
Total nursing time (hours); mean ± SD (range)	38.6 ± 48.9 (0.6 – 216.8)	25.9 ± 8.8 (16.0 – 48.0)	Z = -0.058 p = 0.954	Mann-Whitney U Test
Total labour cost (RM); mean ± SD (range)	278.27 ± 352.37 (4.20 – 1561.20)	186.40 ± 63.43 (115.20 – 345.60)	Z = -0.058 p = 0.954	Mann-Whitney U Test
Total material cost (RM); mean ± SD (range)	25.89 ± 28.95 (6.06 – 216.96)	20.89 ± 13.63 (8.80 – 53.58)	Z = -0.068 p = 0.946	Mann-Whitney U Test
Total cost of intravenous potassium chloride supplementation (RM); mean ± SD (range)	304.17 ± 372.88 (10.26 – 1619.40)	207.29 ± 75.51 (132.80 – 399.18)	Z = -0.489 p = 0.625	Mann-Whitney U Test

n = number of cases. The number of cases referred to cases which used concentrated potassium chloride injection during pre-guideline implementation phase and cases which used premixed potassium chloride injection during guideline implementation phase.

intravenous potassium chloride supplementation was found during the guideline implementation phase compared to pre-guideline phase (RM 207.29 versus RM 304.17).

DISCUSSION

Hyperkalaemia is a main concern in intravenous potassium supplementation and occurs when the rate of potassium supplementation overwhelms intracellular shifts and renal excretion (31–33). The risks are heightened with high infusion rates and high concentration of potassium solutions (11,32). Renal impairment, concomitant drugs which retain potassium, diabetes mellitus and metabolic acidosis are among the contributing factors to hyperkalaemia (33). In this study, hyperkalaemia was present in 3.2% of cases during pre-guideline phase while no hyperkalaemia cases occurred during guideline implementation phase. The main diagnosis of patients during the pre-guideline phase were neurological and cardiac disorders (18%), respiratory disorders (17%) and gastrointestinal disorders (17%). Acid-base disturbances such as acidosis may be present in these disorders which can contribute to hyperkalaemia (12,31). Also, certain medications such as beta blockers, angiotensin receptor blockers, ACE inhibitors and digoxin that may be used in these disorders can lead to hyperkalaemia (12,31). Besides, the levels of potassium during the pre-guideline phase were significantly lower than guideline implementation phase and there were more mild hypokalaemia cases in the guideline implementation phase. This would require less potassium doses in the guideline implementation phase which reduces the risk of overcorrection or hyperkalaemia. Additionally, the hypokalaemia cases in pre-guideline phase involved the use of a significantly higher empirical dose, faster rates of infusion and a more concentrated potassium chloride solution compared to the cases during guideline implementation phase. These could be the reasons for the present of hyperkalaemia cases after the potassium supplementation in the pre-guideline phase. Besides, the cases in pre-guideline implementation were managed by concentrated formulation which required reconstitution before use. There was a possibility of poor mixing of the reconstituted potassium which can cause pooling at the bottom of the intravenous container and lead to unintentionally administering potassium as a bolus despite at a slow infusion rate (34). Conversely, premixed formulations used during the guideline implementation phase does not require manual mixing before administration and are a homogenised solution which reduces the risk of poor mixing (34).

The analysis of effectiveness revealed that there was a higher proportion of cases which achieved normokalaemia during guideline implementation phase compared to cases during pre-guideline implementation phase (71.4% versus 59.1%). Both groups had similar change in the serum potassium level (0.9 mmols/litre), which was consistent with findings from other

studies on intravenous potassium supplementation (35). Despite a significantly higher empirical dose and faster rate of infusion used during pre-guideline phase, it did not give an advantage in effectiveness of intravenous potassium supplementation when compared to guideline implementation phase. The dextrose diluents used to reconstitute concentrated potassium injection in some cases may have caused rebound hypokalaemia (14, 36), but the use of dextrose diluents was not differed significantly between the two phases in the present study. However, the main diagnosis of patients during the pre-guideline phase (cardiovascular disorders, respiratory disorders and gastrointestinal disorders) may again contribute to the challenges in treating hypokalaemia in patients during the pre-guideline phase. Acid-base disturbances such as alkalosis and the use of drugs such as beta 2 agonists can contribute to hypokalaemia (12,31). The significantly lower serum potassium levels among the patients during pre-guideline implementation phase might also make it a challenge to reach normokalaemia as more doses of potassium chloride is required. Additionally, serum magnesium levels were not readily available during this study and possible hypomagnesemia associated hypokalaemia could have been present (12).

Premixed formulations were emphasized in the developed guideline to enhance the safety of intravenous potassium supplementation (37–39). However, the cost of procuring this formulation was a concern as the premixes are more expensive than the concentrated formulation. Nevertheless, premixes offered a possible direct cost saving by reducing nursing time and extra materials for reconstitution (e.g., syringes and needles). Therefore, a decision tree was used to outline the cost implications of using concentrated formulation compared to premixed formulations. For cases that used concentrated formulations during the pre-guideline implementation phase, the potassium injection was reconstituted by nurses, and additional diluent and reconstitution materials were needed. Meanwhile, reconstitution was not required for premixed formulations as this formulation was ready to be administered (37).

The direct cost analysis was conducted separately for mild hypokalaemia cases and moderate to severe hypokalaemia cases as the number of doses may differ according to the level of hypokalaemia. The analysis revealed that labour cost was significantly lower in mild hypokalaemia cases during guideline implementation phase compared to pre-guideline phase. The cost reduction was contributed by a significantly lower total infusion time and removal of drug preparation time during guideline implementation phase whereby premixed formulations were solely used. Despite the concern of a higher material cost from using premixes, the total cost of intravenous potassium supplementation was lower during guideline implementation phase. Similar findings were noted for moderate to severe cases. Although the acquisition cost of premixed formulations was higher than the concentrated formulations, the results revealed that cost savings can be obtained from reduced nursing time and elimination of materials used for reconstitution. These findings were consistent with other studies on costs of premixed formulations in which a reduction in nursing time associated with preparing, administrating and monitoring were seen in these premixes (25,26). There are other potential benefits of eliminating the task of reconstituting, for instance, the nursing time can be directed to other clinical matters such as patient monitoring and nursing care (40). Besides, reconstitution is often carried out at the patient's bedside, posing a risk of contamination and error (41). Thus, premixes formulation has the potential to further reduce costs by improving patient's quality of care and reduction of medication errors (42).

Study Limitations

The developed guideline was implemented in a single private hospital. Thus, the guideline may not be suitable to other institutions particularly government hospitals which have different settings. However, this study provided an insight on safety and effectiveness of the developed guideline in the private hospital. Other institutions may develop their local guidelines to suit their patient population and prescribing practices.

The analysis on safety, effectiveness and cost implications of the developed guideline revealed non-significance differences between the two phases. However, the proportion of hyperkalaemia cases were lower and the proportion of cases achieving normokalaemia were higher during the guideline implementation phase. The total cost of intravenous potassium supplementation was also lower during the guideline implementation phase. The non-significant results may be contributed by the low sample size during the guideline implementation phase for which the sample size required was not achieved. The low sample size was due to the difficulty in obtaining the premixed formulation in Malaysia which required a special import permit. Besides, the guideline implementation phase was conducted during the COVID-19 pandemic for which the number of patients who admitted to the studied private hospital were very limited.

The cost implications analysis of the developed guideline with emphasis of premixed formulation included only direct costs of materials and nursing labour, which was the interest of the studied private hospital in the effort to reduce costs. Therefore, the findings of cost implications may not be generalized to the government sector. Besides, this study did not explore the indirect costs such as cost savings from improved patient's quality of life or costs related to prevention of medication errors.

CONCLUSION

The premixed potassium chloride formulation was not differed significantly from the used of concentrated formulation in the safety and efficacy of hypokalaemia treatment. Considering cost implications, the implementation of the guideline which emphasized on the use of premixed potassium chloride injections revealed a total cost reduction due to reduction in labour costs. The results of this study support the recommendations on implementing a guideline on intravenous potassium supplementation and the use of premixed formulations whenever possible.

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