Peripheral Intravenous Infusion of Potassium Chloride: Effect of Solution Composition on Infusion-Site Pain

Rita Chan and David Armstrong

ABSTRACT

Objective: To test the hypothesis that pain at the site of peripheral intravenous infusion is greater if potassium chloride is administered in sterile water than if it is administered in saline.

Methods: A randomized, double-blind study of infusion-site pain was completed with 36 hospital inpatients with hypokalemia who required 1, 2, or 3 peripheral intravenous infusions of potassium chloride (10 mmol) in 100 mL of IV fluid. Patients were randomly assigned to 1 of 3 groups and were administered potassium chloride in 1 of 3 infusion fluids: sterile water, 0.9% sodium chloride, or 0.45% sodium chloride. Patients rated the degree of pain at the injection site using a 10-point numeric rating scale before the start, at 15 min after the start, and at the end of each of the 3 infusions.

Results: Baseline mean pain scores were similar for all groups. Pain scores in the sterile water group at the end of first, second, and third infusions were significantly higher than those in the 0.9% sodium chloride group (p = 0.003, p = 0.003, p = 0.043, respectively), and were also significantly higher than those in the 0.45% sodium chloride group at the end of first and second infusions only (p = 0.003, p = 0.007, respectively) There were no significant differences between the 0.9% and 0.45% sodium chloride groups.

Conclusion: Peripheral intravenous infusion of potassium chloride produces significantly more pain at the infusion site when administered in sterile water than in saline.

Key words: potassium chloride, IV infusion, pain

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RÉSUMÉ

Objectif : Vérifier l'hypothèse selon laquelle la douleur au point de perfusion intraveineuse par voie périphérique est plus prononcée si le chlorure de potassium est administré dans de l'eau stérile plutôt que dans une solution saline.

Méthodes : Une étude randomisée, à double insu, sur la douleur au point de perfusion a été menée à terme auprès de 36 patients hospitalisés, présentant une hypokaliémie nécessitant une, deux ou trois perfusions intraveineuses par voie périphérique de chlorure de potassium (10 mmol) dans 100 mL de liquide pour perfusion intraveineuse. Les patients ont été répartis au hasard dans l'un des trois groupes de solution pour perfusion : eau stérile, chlorure de sodium à 0,9 % ou chlorure de sodium à 0,45 %. Les patients ont évalué leur douleur au point de perfusion à l'aide d'une échelle de 1 à 10, avant le début de chaque perfusion, à 15 minutes après le début de chaque perfusion et à la fin de chaque perfusion.

Résultats : Les cotes moyennes initiales étaient semblables dans les trois groupes. Les cotes dans le groupe eau stérile à la fin de la première, de la deuxième et de la troisième perfusion étaient considérablement plus élevées que celles dans le groupe chlorure de sodium à 0,9 % (p = 0,003, p = 0,003, p = 0,043, respectivement), et que celles dans le groupe chlorure de sodium à 0,45 %, à la fin de la première et de la deuxième perfusion (p = 0,003, p = 0,007, respectivement). On n'a observé aucune différence significative entre le groupe chlorure de sodium à 0,9 % et le groupe chlorure de sodium à 0,45 %.

Conclusion : La perfusion intraveineuse par voie périphérique de chlorure de potassium est considérablement plus douloureuse au point de perfusion lorsqu'on utilise de l'eau stérile plutôt qu'une solution saline.

Mots clés : chlorure de potassium, perfusion intraveineuse, douleur

INTRODUCTION

Hypokalemia, one of the most prevalent laboratory abnormalities in clinical practice, is defined as a potassium value of less than 3.6 mmol/L. Hypokalemia occurs in over 20% of hospitalized patients.[1] It can be caused by the loss of total body potassium, usually from the gastrointestinal tract as a result of vomiting, diarrhea, or a surgical fistula, or from the kidney as a result of renal disease, diuretic administration, or increased aldosterone production.[2] Hypokalemia can also develop as a result of a shift from extracellular fluid into cells, as seen in patients with alkalosis or with diabetes after the administration of insulin for hyperglycemia.[2] Clinically, patients with mild hypokalemia may have no symptoms, but those with more profound hypokalemia can develop generalized weakness, tetany, and cardiac arrhythmias.[3] In addition, hypokalemia may increase the toxicity of digoxin, whereas prolonged hypokalemia can cause secondary renal tubular damage, which may be permanent.[2]

The treatment of hypokalemia consists of correcting the underlying disorder and replacing the potassium deficit.[4] Oral replacement is preferred,[3] but in patients with severe hypokalemia or when the oral route is not available, controlled intravenous infusion of potassium may be required. Commonly, if rapid replacement is required, intravenous potassium is administered as a series of mini-infusions of potassium chloride (KCl) solution, usually 10 mmol in 100 mL of IV fluid.

Administration of concentrated solutions of KCl (>8 mmol/100 mL) through peripheral veins has been associated with pain at the infusion site.[5,6] Studies[5-8] show that lidocaine, either given as a bolus or added to the KCl infusion, can reduce this local pain significantly, although the routine use of a local anesthetic agent for this purpose is not generally recommended.[5] There are also reports that infusions of 20 mmol of KCl in 100 mL normal saline[9] or 40 mmol of KCl in 100 mL of 5% dextrose in water[7] are well tolerated when given through a peripheral vein, with only occasional patient complaints of discomfort.

At Hamilton Health Sciences, intravenous KCl mini-infusions were traditionally prepared on the ward by nurses using concentrated KCl ampoules (2 mmol/mL) diluted with 0.9% sodium chloride (NaCl). These infusions were generally well tolerated. In an attempt to decrease the risk of serious or fatal medication errors attributable to the inadvertent administration of concentrated KCl injection, all injectable KCl ampoules (2 mmol/mL) were removed from ward stock in March 2000 and replaced with commercially prepared minibags of KCl (10 mmol in 100 mL sterile water) for the administration of intermittent KCl mini-infusions. Since this change of practice, nurses have reported numerous incidents of patients experiencing pain at the infusion site when the contents of these KCl minibags were administered with a peripheral venous cannula. Indeed, in a number of instances patients refused further doses because of the pain experienced during the first infusion.

This randomized double-blind study tested the hypothesis that pain at the site of peripheral intravenous infusion is greater if KCL is administered in sterile water than if KCL is administered in saline.

MATERIAL AND METHODS

Consecutive inpatients with hypokalemia requiring intravenous potassium replacement were enrolled in the study after they gave informed consent. This consent was given while they were in a combined medical and surgical ward. The study protocol was reviewed and approved by the Hamilton Health Sciences/McMaster University Research Ethics Review Board.

Patients who had been prescribed one or more intravenous mini-infusions of KCl (10 mmol in 100 mL) through the peripheral vein were randomized into 3 groups: (i)10 mmol KCl in 100 mL sterile water, (ii) 10 mmol KCL in 100 mL 0.9% sodium chloride (NaCl), and (iii) 10 mmol KCl in 100 mL 0.45% NaCl. The KCl solutions for all 3 groups were prepared by the hospital pharmacy (Hamilton Health Sciences, McMaster University Medical Centre Site, Hamilton, Ontario) in identical mini-infusion bags. The randomization code was available in the pharmacy in case of infusion-related problems.

An intravenous cannula was inserted at least 1 h before the start of the KCl infusion, and all sites were inspected before the first infusion to ensure that there was no obvious pre-existing local pain, tenderness, or phlebitis. Each 100-mL infusion of KCl (10 mmol) was administered over 1 h with an IV infusion pump, and patients received 1, 2, or 3 infusions, as ordered by their physicians. A numeric rating scale (NRS) ranging from 1 (no pain) to 10 (worst pain) was used to rate pain at the infusion site. The nurse asked patients to rate the severity of pain at the infusion site using the NRS before the start, at 15 min after the start, and at the end of each 10-mmol KCl infusion. The nurse, who was unaware of the randomization code, recorded the results on a reporting sheet designed specifically for this study. At the completion of each mini-infusion, the nurse

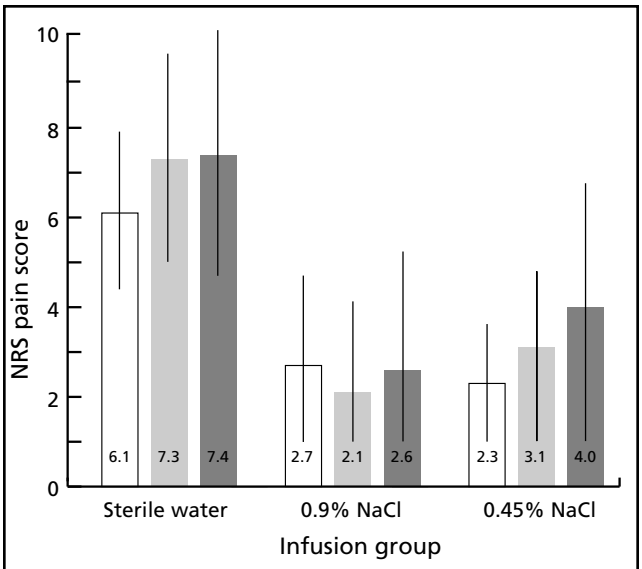

Figure 1. Mean numeric rating scale (NRS) pain scores (95% confidence intervals [vertical lines]) for all 3 study groups after the first (white bars), second (grey bars), and third (black bars) infusion periods.

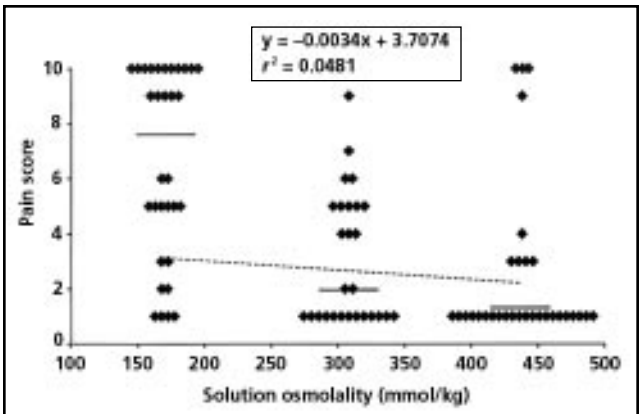

Figure 3. Pain scores (closed diamonds) at the end of the first, second, and third infusions, grouped by the osmolality of the infusion solution: 170 mmol/kg (sterile water), 309 mmol/kg (0.45% saline), and 438 mmol/kg (0.9% saline). The horizontal bars indicate the median pain score for all infusions in each group: 7.5, 2.0, and 1.0, respectively. The dashed line represents the linear regression line for individual pain scores and the solution osmolalities, indicating no significant correlation.

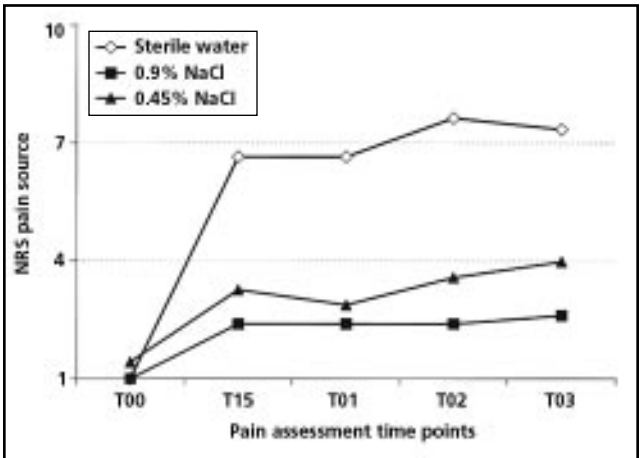

Figure 2. Repeated-measure mean numeric rating scale (NRS) pain scores in the sterile water injection group, the 0.9% saline group, and the 0.45% saline group before the first infusion (T00), at 15 min after the start of the first infusion (T15), at the end of the first infusion (T01), at the end of second infusion (T02), and at the end of third infusion (T03).

inspected the infusion site and recorded any signs of redness or heat. The nurse also recorded the name and dose of any other drug that was being infused through the same cannula at the same time.

The osmolality and pH of the KCl solutions were determined for 3 samples of each group of solutions. Osmolality was determined by freezing-point depression with the Advanced Micro-Osmometer model 3MO Plus (Advanced Instruments, Norwood, Massachusetts). The pH was determined with the Accumet Basic Meter (Fisher Scientific, Hampton, New Hampshire).

A study sample size of 23 for each group was calculated, assuming a 25% reduction in pain and an estimated standard deviation of the difference in pain of 30% ($\alpha = 0.05$, ß = 0.2). Based on these assumptions, 20 patients were to be enrolled in each group. If there were evidence of significant differences in pain responses when half of the patients had been recruited, an interim analysis would be conducted. The aim of the interim analysis was to ascertain whether the occurrence of significantly greater infusion-site pain in one group was sufficient to require that the study be discontinued.

The Kruskal–Wallis statistical test was used to analyze the pain scores of the 3 groups. Pain scores were compared between 2 groups with the Mann–Whitney *U*-test. A $p < 0.05$ was used as the cut-off for statistical significance. Repeated-measures analysis of variance was used for pain assessment at different time points. Linear regression was used to explore the relationship between solution osmolality and pain scores.

RESULTS

After 36 of the intended 60 patients had been enrolled, an interim analysis was conducted. At that time, 7 patients had discontinued the infusion prematurely because of pain. The interim analysis revealed significant differences in pain severity at the

Table 1. Mean Pain Scores for Each Group at Different Times

Time Point	Group	No. of Patients (M/F)	Pain Scores Mean (95% CI)	Range
Time zero	Sterile water	13 (6/7)	1.00 (1.00–1.00)	1–1
	0.9% NaCl	13 (3/10)	1.00 (1.00–1.00)	1–1
	0.45% NaCl	10 (3/7)	1.30 (0.82–1.78)	1–3
	Total	36(12/24)	1.08 (0.96–1.21)	1–3
Time zero + 15 min	Sterile water	13 (6/7)	5.54 (3.23–7.85)	1–10
	0.9% NaCl	13 (3/10)	2.77 (1.23–4.31)	1–8
	0.45% NaCl	10 (3/7)	3.20 (1.18–5.22)	1–8
	Total	36 (12/24)	3.89 (2.77–5.01)	1–10
End of 1st infusion	Sterile water	13 (6/7)	6.08 (4.31–7.85)	1–10
	0.9% NaCl	13 (3/10)	2.69 (0.78–4.61)	1–10
	0.45% NaCl	10 (3/7)	2.30 (0.95–3.65)	1–5
	Total	36(12/24)	3.81 (2.72–4.89)	1–10
End of 2nd infusion	Sterile water	12 (5/7)	7.33 (5.09–9.57)	1–10
	0.9% NaCl	10 (2/8)	2.10 (0.06–4.14)	1–10
	0.45% NaCl	10 (3/7)	3.10 (1.40–4.80)	1–7
	Total	32 (10/22)	4.38 (3.03–5.72)	1–10
End of 3rd infusion	Sterile water	10 (5/5)	7.40 (4.53–10.27)	1–10
	0.9% NaCl	8 (2/6)	2.63 (0.02–5.23)	1–10
	0.45% NaCl	7 (1/6)	4.00 (1.28–6.72)	1–9
	Total	25 (8/17)	4.92 (3.29–6.55)	1–10

M = male, F = female, CI = confidence interval, NaCl = sodium chloride.

end of all 3 infusion periods between the groups (first infusion $p = 0.002$, second infusion $p = 0.002$, and third infusion $p = 0.042$). Based on these results, the study was halted and the remaining 24 patients were not recruited.

At the interim analysis, a total of 36 patients (12 male, 24 female; mean age 57 years, range 18 to 92 years) had been enrolled and had completed the study. Of the 36 patients, 32 received at least 2 consecutive KCl infusions, and of the 32 patients, 25 received 3 consecutive KCl infusions. There was no pre-existing local pain, tenderness, or phlebitis at the site of the infusion, and mean pain scores at the start of the infusions were about equal (Table 1).

Mean NRS scores ranging from 1 (no pain) to 10 (worst pain) before the first infusion, at 15 min after the start of the first infusion, and at the end of the first, second, and third infusions are shown in Table 1. Although there was no significant difference in the mean numeric score before the first infusion, at all other assessment time points mean pain scores were higher in the sterile water group (Figures 1 and 2). Comparisons between the sterile water and 0.9% NaCl groups showed significant differences at the end of first (NRS difference 3.33, $p = 0.003$), second (NRS difference 5.23, $p = 0.003$) and third (NRS difference 4.77, $p = 0.043$) infusions. Differences in pain scores between the sterile water group and 0.45% NaCl group were significant only after the first (NRS difference 3.78, $p = 0.003$) and second (NRS difference 4.23, $p = 0.007$) infusions; no significant difference was found at the end of the third infusion (NRS difference 3.40, $p = 0.07$). The pain scores for the 2 saline groups never differed by more than 1.43 NRS divisions and did not show any significant differences at any time points.

The pH of the 3 KCl solutions was the same (5.4 ± 0.1). The osmolality of KCl in sterile water was 170 mmol/kg; in 0.45% NaCl, 309 mmol/kg; and in 0.9% NaCl, 438 mmol/kg. There was no linear relationship between solution osmolality and pain score ($r^2 = 0.0481$) (Figure 3).

DISCUSSION

This study showed that peripheral intravenous KCl infusion caused significantly more pain at the infusion site when administered in sterile water than in saline. The exact mechanism of infusion-related pain and phlebitis is not known. Irritation, inflammation, and damage to the venous endothelium can be caused by the inherent chemical property, pH, or osmolality of the infusate.[10]

In the current study, the concentrations of KCl and pH were the same in all 3 groups of solutions. The greater pain experienced with infusions of KCl in sterile water could be due to the difference in the osmolality of the final solutions of KCl because of its dilution with different IV fluids. The effect of infusate osmolality on infusion pain is not a well-researched phenomenon,

although the incidence of phlebitis after infusions of hypertonic solutions with osmolalities higher than 600 mmol/kg has been reported for solutions of parenteral nutrition amino acids[11] and with some anesthetic agents.[12] The osmolality of body fluids is close to 285 mmol/kg.[2] Little has been reported on the effect of hypotonic solutions, except the well-known fact that a solution of 0.4% NaCl, which has an osmolality of about 130 mmol/kg, causes hemolysis.[13] The data from the current study suggested that a hypotonic solution (10 mmol KCL in sterile water, osmolality 170 mmol/kg) is more irritating than a hypertonic solution (10 mmol KCL in 0.9% NaCl, osmolality 438 mmol/kg) when administered through a peripheral vein. However, the range of osmolalities studied was too small to allow any definitive conclusions to be drawn.

Other limitations of this study were the small number of patients and other risk factors not taken into account, such as the cannula used, the anatomical location of the cannula, and the duration of cannulation, which also affect pain at the infusion site.[10,14]

Given that hypokalemia is a common occurrence in hospitalized patients and that severe hypokalemia can be life-threatening, it is important that intravenous potassium replacement be carried out with a minimal chance of infusion failure caused by phlebitis, extravasation, or patient refusal because of intolerability. It is also of paramount importance that patients' discomfort be kept to a minimum. This study demonstrated that a KCl solution administered as a mini-infusion through a peripheral vein should not be diluted with sterile water for injection.

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Rita Chan, BScPharm, MSc, is a pharmacist associated with the Inpatient Pharmacy and Digestive Diseases and Surgery Program, McMaster Site, Hamilton Health Sciences, Hamilton, Ontario.

David Armstrong, MA, MB BChir, is a physician in the Digestive Diseases and Surgery Program, Hamilton Health Sciences, Division of Gastroenterology, McMaster University, Hamilton, Ontario.

Address for correspondence:
Rita Chan
Inpatient Pharmacy, McMaster Site
Hamilton Health Sciences
1200 Main Street West
Hamilton ON
L8S 4J9

e-mail: chanr@hhsc.ca

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