Cover Page for Protocol

Official Title:	The Impact of 4% Sodium Bicarbonate Additive During Potassium Chloride Replacement on Pain and Incidence of Phlebitis for Adult Patients in a Medical Surgical Unit: A Randomized Double Blinded Controlled Study
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Title: The impact of 4% sodium bicarbonate additive during intravenous Potassium Chloride replacement on pain and incidence of Phlebitis for adult patients in a Medical/Surgical unit: A randomized controlled double blinded study.

Problem Statement and Specific Aims:
According to the National Council on Potassium in Clinical Practice, potassium depletion is one of the most common electrolyte abnormalities found in the clinical setting (Cohn, Kowey, Whelton, & Prisant, 2000). Hypokalemia has been found to affect between 20-37% of hospitalized patients depending on disease process (Crop, Hoorn, Lindemans, & Zietse, 2007; Hemstreet, Stolpman, Badesch, May & McCollum, 2008; Widodo, Setiawan, Chen, Nainggolan, & Santoso, 2006). In addition, epidemiologic research has found that hypokalemia not only can result from an underlying disease but is frequently acquired in the hospital due to its high association with gastrointestinal losses and use of diuretics (Crop et al., 2007). Therefore, replacement of potassium becomes a common practice carried out by Medical/Surgical nurses caring for patients in acute hospitals. Although oral potassium replacement is an option, patients often require rapid replacement or are unable to be replaced orally. Once intravenous (IV) potassium is initiated, Medical/Surgical nurses are faced with patients experiencing chemical/infusion phlebitis and pain at the catheter insertion site regardless of using slow infusion rates due to the acidic pH of the solution. This results in Medical/Surgical nurses seeking evidence-based options to reduce these further complications. Currently, the use of lidocaine with IV potassium chloride has been found to reduce pain during infusion (Lim, Khoo, & Tweed, 1992; Morril & Katz, 1988; Pucino et al., 1988); however lidocaine has also been linked to chemical phlebitis (Bassan & Sheikh-Hamad, 1983) and does not assist with preventing the complications from infusing acidic solutions. Therefore, this study is interested in evaluating the use of sodium bicarbonate additive as a neutralizing agent to potassium chloride infusion.

The purpose of this study is to examine the impact 4% sodium bicarbonate additive during intravenous potassium chloride replacement for adult patients in three Medical/Surgical units. Using a randomized controlled blinded experimental study design, patients who are 21 years or older and alert, awake, and oriented at time of enrollment and have been ordered intravenous potassium chloride replacement will be recruited from three Medical/Surgical units during the first 24-48 hours of their admission.

The specific aim of the study is:

Aim 1: To compare patient outcomes (phlebitis, pain at peripheral IV insertion site, frequency of changing IV access, and time for administration) between the experimental (4% sodium bicarbonate additive during peripheral intravenous potassium chloride replacement therapy) and control (standard of practice of no 4% sodium bicarbonate additive during peripheral intravenous potassium chloride replacement therapy) groups.

Aim 2: To compare number and type of nursing interventions done during peripheral IV potassium replacement therapy between the experimental (4% sodium bicarbonate additive during intravenous potassium chloride replacement) and control (standard of practice of no 4% sodium bicarbonate additive during peripheral intravenous potassium chloride replacement therapy) groups.

Aim 3: To compare attrition rates and reasons between the experimental (4% sodium bicarbonate additive during peripheral intravenous potassium chloride replacement therapy) and control (standard of practice of no 4% sodium bicarbonate additive during peripheral intravenous potassium chloride replacement therapy) groups.

Significance:
Hypokalemia, or the low concentration of potassium (below 3.5 mmol/l), is a condition that can result in serious adverse effects including disturbances in cardiac conduction along with muscle, kidney,

gastrointestinal tract, genitourinary tract, respiratory, and endocrine dysfunction (Asmar, Mohandas, & Wingo, 2012; Hemstreet, et al., 2008). Hypokalemia is typically a result of chronic medical conditions such as reduced intake of potassium, chronic diuretic therapy, diarrhea, short bowel syndrome, vomiting and burns. Although potassium can be replaced orally, IV potassium chloride is utilized in patients that need rapid replacement, are showing clinical signs of low potassium, or patients who are unable to orally ingest the replacement. Potassium should always be diluted and slowly administered to reduce the likelihood of pain from inflammation of the vein or phlebitis. (Pharmacology for the Prehospital Professional, 2011). Yet, even at slow rates of 10 mEq/h phlebitis and pain have been reported in 60% of patients (Stephens et al., 1976).

Peripheral venous cannulation (PVC) is a common procedure carried out in hospital to allow rapid and accurate administration of medication (Endacott et al., 2009). In replacing Potassium intravenously, nurses need to have intravenous access. In WKBH 3 South/3 North/4 South Medical-Surgical Telemetry units, nurses often receive orders for Potassium replacement through Intravenous route. The majority of these patients have peripheral intravenous access. The intravenous access is often started in the Emergency Department and continued once the patient is admitted. The peripheral intravenous site is being assessed per protocol for phlebitis once per shift and as needed.

Once the Physician orders the Potassium replacement intravenously, the Pharmacist prepares the medication. The nurse then, starts the infusion via the peripheral intravenous access. Nurses receive complaints of burning sensation or pain from patients as soon as the infusion is started. The nurse then would try to get an order for Neut (4 % sodium bicarbonate additive solution) to be added to the Potassium Chloride solution with the goal to minimize pain during infusion. Neut (4% sodium bicarbonate additive solution) is a neutralizing additive solution, a sterile non-pyrogenic solution of sodium bicarbonate in water for injection. It is administered by the intravenous route only after addition as a neutralizing agent to an acidic large volume parenteral solution. It is indicated for use as an additive to raise the pH of acid solutions administered intravenously to reduce the incidence of chemical phlebitis and patient discomfort due to vein irritation at or near the site of infusion. (APP Pharmaceuticals, 2008). Previous studies have concluded that one of the causes of infusion phlebitis was the pH of the solution (Lewis and Hecker, 1985; Kuwahara, et al 1998). A study conducted by Fujita et al 2000, confirmed that with the use of 7% Sodium Bicarbonate, moderate phlebitis was only experienced by 6% of the patients. Although cardiovascular abnormalities are rare when KCl is administered at an infusion rate of 10mEq/hour, phlebitis and pain reportedly occur in 60% of patients (Stephens et al 1976)).

The mechanism by which KCl causes pain and phlebitis upon I.V. administration is not known. A study by Morrill and Katz, 1988 provided evidence that Lidocaine in small doses is effective in reducing KCl-induced pain but no literatures have been found on the use of 4% Sodium Bicarbonate to reduce pain or phlebitis during intravenous Potassium replacement. This study will test the effects of 4% Sodium Bicarbonate additive during intravenous potassium chloride replacement. This study will also look at efficacy of 4% Sodium Bicarbonate in reduction and prevention of pain and phlebitis on patients receiving intravenous Potassium Chloride replacement.

Methods:

Staff Education: will include, but not be limited to: (1) an introduction to the study; (2) how potential participants will be screened (i.e. only patients that have been ordered peripheral intravenous potassium chloride replacement therapy as part of their care which is regardless of research); (3) how participants will be identified via sticker on chart; (4) how the intervention will be rolled out in collaboration with pharmacy and the medical staff; (5) how data collection will occur; and (6) who to contact if there are any questions about the study.

Recruitment (3 means):

(1) The resource nurse will be provided a screening tool (please see attached screening flyer) to assess for potential participants on admission. The resource nurse will inform the principal investigator and/or designated key personnel either by phone or email that a potential participant

has been admitted. No identifying information will be provided. The principal investigator or designated key personnel will then talk with the resource nurse while on the unit in order to determine the potential participant's location on the unit and the direct patient care nurse assigned to her or him. The principal investigator or designated key personnel will then attempt to enroll the potential participant after: (a) the direct patient care nurse initiates contact with the potential participant (please see script); and (b) potential participant has agreed to meet with the principal investigator or designed key personnel.

(2) The principal investigator will meet with the resource nurse or patient care supervisor (PCS) on 3 South/3 North/4 South to determine if any patients meet the inclusion criteria (please see attached screening flyer). If the principal investigator identifies a potential participant she will attempt to enroll the potential participant after: (a) the direct patient care nurse initiates contact with the potential participant (please see script); and (b) potential participant has agreed to meet with the principal investigator.

(3) The designated key personnel will go to 3 South/3 North/4 South on a daily bases Monday through Friday and meet with the resource nurse or patient care supervisor (PCS) to see whether potential participants are on the unit, and ask for their room numbers and staff nurse assigned to them. The designated key personnel will then attempt to enroll the potential participant after: (a) the direct patient care nurse initiates contact with the potential participant (please see script); and (b) potential participant has agreed to meet with the designed key personnel.

Enrollment Process:

(1) The study will be explained, consent and HIPAA; in either English or Spanish (which will be determined by the participant's personal choice), will be obtained (please see attached consent) after the principal investigator or designated key personnel has answered all questions. The potential participant will be provided with about 10 minutes of individual time to review the consent. Each participant will be provided a copy of their signed consent (please see attached).

(2) Once enrolled the principal investigator or designated key personnel will: (a) contact the pharmacy to inform them that a new participant has been enrolled in the research study; (b) place a sticker on the chart of the participant (study number and enrollment date); and (c) place the participant (medical recorder number and study number provided by pharmacy) into the enrollment log. The pharmacy research team member will then randomize the participant into either the experimental group (4% sodium bicarbonate additive during peripheral intravenous potassium chloride replacement therapy) or the control group (standard of practice of no 4% sodium bicarbonate additive during peripheral intravenous potassium chloride replacement therapy) based on a randomization table. The randomization table will be generated by the statistician research team member after IRB approval is obtained by use of the statistical package nQuery. The pharmacy research team member will label the potassium replacement IV bags with a sticker to identify them as study participants. This will include the standard of practice of labeling the IV bags as potassium replacement and also a label stating "neut study participant" but without the designated grouping in order to maintain blinding. In order to maintain integrity of data and reduce bias the participant and direct patient care nurse will not be informed of randomization results. The pharmacy research team member will maintain a record of randomization that will be provided to the principal investigator.

    a. Participants enrolled in the control group will receive standard of practice which is intravenous potassium replacement without the 4% sodium bicarbonate additive at the rate ordered by the ordering physician or ARNP for peripheral intravenous potassium chloride replacement therapy which will be part of the care of the patient regardless of research, and based on the WKBH policy of potassium chloride infusion of no more than 100ml/hr. Pharmacist prepares, as standard of practice, each bag of 100 ml normal saline (NS) with 10mEq potassium chloride.

b. Participants enrolled in the experimental group (4% sodium bicarbonate additive during peripheral intravenous potassium chloride replacement therapy) will receive the additive after pharmacy and/or the designated key personnel (Dr. Soto) coordinates the ordering of 4% sodium bicarbonate additive during peripheral intravenous potassium chloride replacement therapy. Pharmacist prepares, when ordered as standard of practice, each bag of 100 ml NS with 10mEq Potassium Chloride and 5 ml of 4% sodium bicarbonate additive, therefore, this practice will be used for the experimental group. The rate of peripheral intravenous potassium chloride replacement therapy will be ordered by the ordering physician or ARNP, for IV potassium chloride replacement therapy which will be part of the care of the patient regardless of research, and based on the WKBH policy of potassium chloride infusion of no more than 100ml/hr.

Data Collection:

(1) Demographics (please see attached) will be collected by the principal investigator or designated key personnel after enrollment of patient.

(2) peripheral intravenous potassium chloride replacement therapy (please see attached) data collection form: assessment of peripheral IV insertion site for phlebitis, using the VIP tool, and pain, using the Likert 11 point scale will be collected at baseline (prior to any peripheral intravenous potassium chloride replacement therapy), at 15 minutes after infusion started, every hour until peripheral intravenous potassium chloride replacement therapy is complete, and then at completion of replacement.

a. *Visual infusion phlebitis (VIP) tool*: The VIP tool was developed by Jackson (1998) to assess intravenous sites for early signs of infusion phlebitis. The tool was developed to assess intravenous sites daily; when bolus injections are administered, intravenous flow rates are checked or altered; and when solution containers are changed (Jackson, 1998). Inter-rate reliability was established as 0.85 or greater (unpublished data, Gallant, 1998, 2002) and content validity through consensual agreement was established (Gallant & Schultz, 2006).

b. *Pain, Numerical Rating Scale (NRS) Likert 11-point scale*: pain assessment using the Likert 11-point scale of 0-10 with 0 being no pain, 5 being moderate pain, and 10 being the worst possible pain is the current standard of practice at WKBH for assessing pain in adult patients. Past research has shown that the NRS is sensitive to treatments that are expected to affect pain intensity (Chesney & Shelton, 1976; Kaplan, Metzger, & Jablecki, 1983; Keefe, Schapira, Williams, Brown, & Surwit, 1981; Seymour, 1982; Stenn, Mothersill, & Brooke, 1979) and is easy to use in a variety of patients (Melzack & Torgerson, 1971).

c. Peripheral intravenous potassium chloride replacement therapy (please see attached) data collection form will also include: administration start and stop time; nursing interventions performed (i.e. IV site change, slowed rate, request for 4% sodium bicarbonate additive); and pain medication use prior or during intravenous potassium chloride replacement therapy.

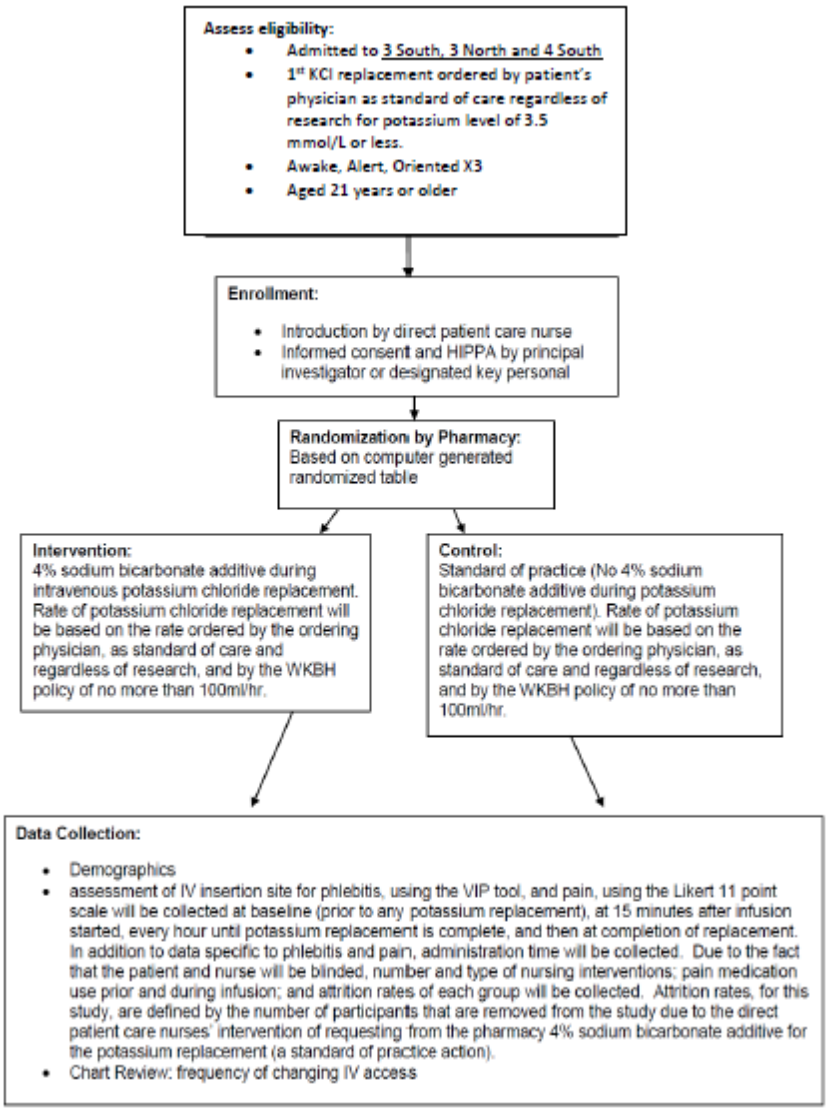
d. Direct patient care nurses (during the education prior to the study) will place the collected peripheral intravenous potassium chloride replacement therapy data collection form into the provided envelop then seal it and place it in to the box labeled “research study’ that will be found in the medication room.

i. Due to the fact that the patient and nurse will be blinded, number and type of nursing interventions and attrition rates of each group will be collected. Attrition rates, for this study, are defined by the number of participants that are removed from the study due to the direct patient care nurses’ intervention of requesting from the pharmacy 4% sodium bicarbonate additive for the peripheral intravenous potassium chloride replacement therapy which is a standard of practice action for patients complaining of pain during infusion

or requesting for the infusion not to have an additive. In this case, or in any adverse event, the pharmacist will unblind the patient and the nurse by revealing which group the patient is in.

Data Storage:

(1) All data collection sheets will be coded and not include identifying information.
(2) The enrollment log(s) will be kept by the research team members in their locked BHSF office drawer or filing cabinet. At the end of the study the enrollment logs will be housed in the principal investigator's locked office drawer or filling cabinet. Enrollment logs will be kept separate from data collection. Peripheral intravenous potassium chloride replacement therapy data collection will be sealed in an envelope and placed in the designated 'research' box in the medication room. Then on a weekly basis the envelopes will be collected by a member of the research team and given to the co-investigator (Julie Lamoureux). Data entry into the BHSF password protected computer system will be done by the designated research team member and then all hard copies will be housed in the principal investigator's BHSF locked office or filling cabinet.
(3) All demographic and chart review data will be given to the co-investigator (Julie Lamoureux). Data entry into the BHSF password protected computer system will be done by the designated research team member and then all hard copies will be housed in the principal investigator's BHSF locked office or filling cabinet.
(4) At the end of the study, all data will be housed in the principal investigator's locked BHSF office drawer or filing cabinet.
(5) All electronic data will be password protected on the BHSF computers of the research team.
(6) All data will only be accessible by the research team.



Instruments:

Demographic form: data obtained by the participant about her or his self.

Visual infusion phlebitis (VIP) tool: The VIP tool was developed by Jackson (1998) to assess intravenous sites for early signs of infusion phlebitis. The tool was developed to assess intravenous sites daily; when bolus injections are administered, intravenous flow rates are checked or altered; and when solution containers are changed (Jackson, 1998). Inter-rate reliability was established as 0.85 or greater (unpublished data, Gallant, 1998, 2002) and content validity through consensual agreement was established (Gallant & Schultz, 2006).

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Participants:

Participants will be recruited from one adult acute care hospital (West Kendall Baptist Hospital) within Baptist Health South Florida (BHSF) health system; one of the largest not-for-profit hospital systems in South Florida. Initial screen will occur during the first 24-48 hours of the Medical/Surgical admission. Inclusion criteria: (1) admitted to the Medical/Surgical unit within the last 24 to 48 hours; (2) alert, awake, and oriented times three; (3) aged 21 years old and greater; (4) receiving her or his first peripheral intravenous potassium chloride replacement therapy as ordered by her or his physician or ARNP as part of her or his care and regardless of research; and (5) potassium level of 3.5 mmol/L or less. Exclusion criteria: (1) patients who have been in the Medical/Surgical unit for more than 48 hours; (2) altered mental status defined as not being alert, awake, and oriented times three; (3) patients who have already received intravenous potassium chloride replacement during the current admission and with the current IV access; (4) patients receiving intravenous Potassium replacement therapy through a central line ; and (5) patients that are not ordered potassium replacement by her or his physician as part of their care while hospitalized.

The literature indicates that the rate of phlebitis for IV administration of toxic substances is substantially higher than with non toxic substances (OR = 5.1). We computed the sample size needed in relation to the main objective of comparing the rate of phlebitis in subjects being administered a toxic substance (Potassium IV replacement) to the rate of phlebitis in subjects receiving the same substance but with the addition of 4% sodium bicarbonate additive (to neutralize the toxicity). Using an alpha of 0.05 in a logistic regression assuming the occurrence of phlebitis without 4% sodium bicarbonate additive at 0.15 and a multiple correlation between the covariates of 0.2, a total sample size of 150 (75 patients per group) would have a power of 80% to detect an odds ratio of 5.0.

This sample size will yield an 80% power to detect a difference as little as 1.5 unit on a 10-point rating scale with unequal variances between the two groups, assuming a ratio of 2.75 between the groups' standard deviations in a Satterthwaite t-test at a two-sided 0.05 level of significance. It will also yield a power of 80% to detect an effect size of 0.46 in the length of administration using a t-test with a 0.05 two-sided level of significance. A sample size of 75 per group will also yield 80% power to detect a probability of 0.632 that an observation in the experimental group is less than an observation in the control group for the frequency of changing the IV, the number of nursing interventions and the rates of attrition using Wilcoxon rank-sum test with a 0.05 two-sided significance level. In addition, considering that currently about 85 patients per month receive IV potassium replacement on the Medical/Surgical floor, it is expected that the research team will be successfully able to enroll the needed sample. Although by power analysis a total of 150 participants is needed, in order to control for confounding variables the sample will be 200 (100 in each group).

Other Pertinent Information:

Standard of Practice for Potassium chloride replacement therapy: The Physician or ARNP evaluates the Potassium level of the patient and orders potassium replacement therapy for potassium level of 3.5 or below. The amount of replacement of potassium intravenously is determined by the patient's physician or ARNP based on patient's condition and potassium level as standard of practice and the order is provided to the direct patient care nurses and pharmacy. Patients with peripheral IV access may be ordered to receive intravenous potassium replacement therapy of 10 mEq/100 ml Normal Saline bag, ordered as one or multiple doses depending on the potassium level and patient's condition. The peripheral intravenous site is being assessed per protocol for phlebitis once per shift and as needed. During potassium chloride intravenous replacement direct patient care nurses can initiate nursing interventions including but not limited to: changing IV site, slowing rate of infusion, and requesting from the patient's physician or ARNP an order for 4% sodium bicarbonate additive solution.

Study Procedures covered: Those participants in experimental group who will receive up to 4 doses of 4% sodium bicarbonate will not be charged for those experimental doses. The Academy of Medical-Surgical Nurses (AMSN) is sponsoring this study and the cost of 4% sodium bicarbonate to Pharmacy will be covered by AMSN.

Limitations
This study has some limitations. Firstly, the sample will include patients in a Medical/Surgical units admitted for various reasons which can result in varying intravenous drug therapy. For this reason participants will be randomized and only those that have been on the unit for 24-48 hours will be approached for enrollment. Secondly, the direct patient care nurses will be assessing phlebitis and pain at IV insertion site which can reduce fidelity of data collection. Therefore, a reliable and valid tool will be used along with initial education and additional education at six months will be provided by the research team.

Potential Benefits of the Proposed Research to the Subjects and Others
While there is no outward benefit to the participant for taking part in the study, the knowledge gained from this study will add to the body of nursing knowledge specific to Medical/Surgical nursing as it relates to intravenous therapy and patient comfort. This study will test how 4% sodium bicarbonate additive could help reduce or prevent phlebitis and pain which is hospital acquired conditions. In addition, it is possible that participants will feel a sense of satisfaction in helping determine if an inter-collaborative pharmacist and nurse-drive prevention strategy can help with reducing the rate of phlebitis and pain at the IV insertion site of patients receiving potassium replacement. If the result of this study is positive, it could be used as evidence that hospital acquired phlebitis could be prevented or reduced with great implications to nursing practice in the decrease of frequency of changing peripheral access, cost-effectiveness and possible harm to the patient.

Tentative Plan for Data Analysis
Descriptive statistics for demographic and baseline variables will be computed for both groups using frequencies and proportions for categorical variables and means, medians, standard deviations and ranges for numerical variables. To compare the differential rate of phlebitis between the two groups, we will compute the odds ratio (with a 95% confidence interval) using logistic regression. Although the randomization process aims at eliminating the differences between groups, if the groups end up significantly different in baseline variables, those variables will be controlled in the logistic regression. It

is hypothesized that the variances in pain scales will be different between the two groups. Therefore, to compare the pain level between the groups, we plan on using a Satterthwaite t-test. An independent t-test will be used to compare the length of administration per unit of the medication. All other variables will be compared between groups using Wilcoxon rank-sum tests. All tests will be performed at the 0.05 level of significance unless otherwise specified using Stata 12.1 (StataCorp, Texas).

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