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Editorial

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Depression in Dialysis

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When was the last time you talked to your dialysis patient about depression? And what prompted you to start the conversation?

It may be that our patients are not talking to us about the way they feel regarding the treatments we offer them, but they are definitely talking about it amongst themselves online; On a facebook page named "Dialysis suck," and a website titled "Ihatedialysis.com", where dialysis patients are able to express the distress and discomfort, the sadness and loneliness they feel while on dialysis.

One dialysis patient writes about her experience in the first 4 months of dialysis from the latter website:" *I had dialysis yesterday, and it seemed endless. It has been hurting, stinging, throbbing, infiltrating, fistula grams, balloons, rogue beings, narrow arteries, I went to bed crying and I woke up crying. I am as alone as I can ever remember", When I am not at dialysis, I am spending my days off on the phone with doctors or on here or something like that, documenting the latest damage so I never get a break. There is no joy to offset this experience".*[1]

PREVALENCE OF DEPRESSION

Depression is the most common psychiatric diagnosis in dialysis patients.[2] Watnick et al found that depressive symptoms are very common at the start of dialysis therapy, as up to 44% of the patients she screened with the Beck Depression inventory (BDI) were depressed.[3] It is estimated that up to 30% of the dialysis patients suffer from major depression.[4] In comparison, a study conducted by the CDC, which surveyed the prevalence of depression in 2006-2008 in the general population, found that amongst 235,067 adults (in 45 states, the District of Columbia [DC], Puerto Rico, and the U.S. Virgin Islands), 9.0% met the criteria for current depression, including 3.4% who met the criteria for major depression. By state, age-standardized estimates for current depression ranged from 4.8% in North Dakota to 14.8% in Mississippi.[5]

BACK IN TIME

In 1969, Beard interviewed 14 dialysis patients who were in the process of being assessed for a kidney transplant.[6] He tells the story of each of them, their personalities and feelings towards their illness; he described their intimate experiences with fear of imminent death. Some of them controlled this anxiety by plain denial. After denial however, came sadness and hopelessness:

"Patients with renal failure fear that their lives will be cut short by an untimely death, and as we listen closely we also hear these same patients express their fears that even if they live, their lives may not be acceptable. This fear of death, coupled with a fear of life, is the dilemma of the patient with chronic renal failure."

Later, in 1971, Abram et al sent out questionnaires to 201 dialysis centers in the United States,[7] surveying suicide attempts, withdrawal, death due to non compliance and accidents. 127 questionnaires were returned, and they included 3478 living and dead dialysis patients. Notably, the events questioned, were higher amongst patients getting

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in center dialysis, as compared to those getting dialyzed at home. He concluded that even when not including non-compliance, the incidence of suicide is 100 times more than the general population.

HIGHER MORBIDITY AND MORTALITY FOR DEPRESSED PTS ON HD

Over the years there have been many studies, which have raised our awareness and shown increased morbidity and mortality in ESKD patients who report having depressive symptoms,[8] or those who are diagnosed with clinical depression.[9]

Moreover, several studies have shown a connection between depression and physiological changes, increasing the depressed patient's risk for disease; Some of those discoveries include a higher c-reactive protein levels in depression[10] an increased risk for cardiovascular disease,[11] enhanced platelet and endothelial activation,[12] alterations in attention and cognitive functions[13] and dysregulation of the hypothalmic-pituitary-adrenal axis.[14]

Combining the above with the non -compliance associated with depression,[15] we can begin to understand why the depressed dialysis patient has a higher morbidity and mortality.[16]

HOW MUCH IS IT COSTING US?

Arneson et al were able to create an algorithm to estimate the magnitude of fluid overload treatment episodes in inpatient, hospital observation, and ED settings for the Medicare hemodialysis population, focusing on episodes that might be preventable. They included all U.S. ESKD patients who were receiving hemodialysis with Medicare as the primary payer, and who survived at least 90 days after ESKD onset (January 1, 2004 - December 31, 2006.)

They found that the total costs for the episodes identified in the study cohort, over the 2.5-year follow-up period were approximately $266 million. The average cost was $6,372 per fluid overload treatment episode; (Inpatient episodes $7,171, hospital observation $1,947, emergency department $1,326).[17]

WHAT CAN WE DO?

Due to the high prevalence of depression in dialysis patients, it would be reasonable to screen all patients for depression using questionnaires such as BDI or short form 36. Those with concerning results may benefit from initiating treatment. CBT has been shown to be effective,[18,19] physical activity[20] and anti-depressants,[21] while closely monitoring the patients for side effects. Recently, the science of a dog's capability to treat depression and PTSD is widening, and we should consider using those loving animals with patients in dialysis.

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Editorial

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The G Protein-Coupled Estrogen Receptor (GPER-1): A Novel Regulator in the Kidney

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Gender has a crucial influence on incidence and prognosis of chronic and acute kidney diseases since women generally have a lower morbidity and mortality compared to men.[1,2] Several studies have reported the capability of estrogen to promote homeostatic and protective effects in the kidney *via* a pregenomic mechanism that is mediated by G protein-coupled receptor 30 (GPR30), but not by classic Estrogen Receptors (ER), ERα or ERβ.[2] GPR30 was first cloned as an orphan receptor from a Burkitt's lymphoma cell line[3] and then confirmed in other cell lines.[4] Prior studies have demonstrated that GPR30 is a specific, high affinity, G_s-coupled estrogen membrane receptor activated by naturally occurring and synthetic estrogens and antiestrogens including estradiol-17β, G1, tamoxifen, ICI182,780, Genestein and Bisphenol A, but not by cortisol, progesterone or testosterone in both mammals and fish.[5-15] Thus, GPR30 was designated G protein-coupled estrogen receptor-1 (GPER-1) by the International Union of Pharmacology in 2007.[16]

GPER-1 is highly expressed in kidney tissues albeit with differences regarding its subcellular distribution, which may in part be due to differences in methodological approaches in measuring its expression and activity.[17-21] Recently, Filardo and coworkers evaluated the topographic mapping of GPER-1 expression in renal tubules using dual immunostaining of the receptors and specific markers for distinct tubules in tissue section.[22] The results revealed that GPER-1 immunoreactivity is mainly localized in the distal convoluted tubules and the loop of Henle, and to a lower level in the proximal convoluted tubules.[22] Interestingly, the subcellular distribution pattern of GPER-1 in these tubules is distinct: GPER-1 in the distal convoluted tubules and the loop of Henle mainly resides in the cytoplasm with less GPER-1 in the basolateral plasma membrane, whereas GPER-1 in the proximal convoluted tubules is primarily located in the basolateral membrane.[22] Similar pattern for GPER-1 expression has been observed in male rat renal epithelia.[19] Intriguingly, subcellular distribution of GPER-1 is modulated during the estrus cycle. During the secretory phases of the estrus cycle, GPER-1 is upregulated on cortical epithelia and localized to the basolateral surface during proestrus and redistributed intracellularly during estrus. GPER-1 is down-modulated during luteal phases of the estrus cycle with significantly less receptors on the surface of renal epithelia.[22] Lindsey and colleagues reported that GPER-1 imunoreactivity is predominantly localized to the apical surface of the proximal tubule and minimally to the glomerulus but not to the distal tubules in female hypertensive rat.[20] Differences in the subcellular distribution pattern and topographic localization of GPER-1 in distinct renal tubules may suggest that GPER-1 plays differential roles in mediating fluid and electrolyte homeostasis, and that pathological conditions such as hypertension may influence subcellular translocation of GPER-1 in renal epithelia.

Accumulating evidence has shown multiple roles for GPER-1 in the kidney in the

context of physiological and pathological conditions. The specific GPER-1 agonist, G1,[15] estradiol-17β (E2), and ICI 182,780 (the ER antagonist and GPER-1 agonist)[12] have been reported to increase acute Ca^{2+} concentration and H^+-ATPase activity intracellular calcium signals in microdissected renal tubule segments and isolated intercalated cells but not in similar explants and cell cultures isolated from GPER-1-deleted mice, suggesting a role for GPER-1 in regulating Na^+ and Ca^{2+} reabsorption in renal tubules and subsequently affecting fluid retention.[21] Prior studies revealed that G1 and estradiol-17β induce vasodilation in female mouse, pig and rat and vasoconstriction in male rat.[23] A recent study demonstrated that GPER-1 exerts beneficial effects on preventing excessive mesangial matrix production and modulates mesangial cell migration.[2] Chappell and co-workers have shown that GPER-1 colocalizes with megalin in renal proximal tubules and that G1 ameliorates salt-induced renal injury in female mRen2. Lewis mice independently of changes in systolic blood pressure.[20] Estrogen has been shown to ameliorateischemic glomerular endothelial hyperpermeability *via* a GPER-1-mediated mechanism.[1]

Collectively, while more work is required to elucidate the physiological significance of GPER-1 modulation in the kidney, current findings strongly suggest that GPER-1 in the kidney facilitates selective reabsorption of water and electrolytes, mediates renal vascular activities and mesangial cell behavior and reduces proteinuria and oxidative stress.

CONFLICTS OF INTEREST: None.

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Hemodialysis Infection Prevention using Polysporin Ointment with Shower Technique in Satellite Units (HIPPO-SAT) Pilot Study Design

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ABSTRACT

Background: Hemodialysis patients are often advised not to shower if they have a central venous catheter (catheter). We developed a shower technique catheter protocol for hemodialysis patients with healed catheter exit sites, designed to permit showering but not increase catheter-related infection risk.

Research question: Is it feasible to conduct a randomized control trial comparing the rate of catheter related bacteremia in adult satellite hemodialysis patients using the shower technique protocol *versus* standard catheter care alone with 6 month follow up?

Study Design: This pilot study is a multi-centre randomized control trial. Eligible participants will be randomized to shower technique protocol *versus* standard care after meeting predefined criteria to confirm healed tunneled catheter exit site.

Primary Outcome: Feasibility will be determined by 5 outcome measures: 1) accuracy of the catheter related bacteremia rate documentation in the satellite hemodialysis centre setting, percentage of patients 2) screened, 3) recruited, 4) educated successfully in the shower technique protocol (intervention arm), and 5) treatment contamination of study groups.

Study Setting: In 2 academic and 3 community based satellite hemodialysis centres in south central Ontario, Canada.

Patient Population: Adult satellite hemodialysis patients dialyzing *via* tunneled central venous catheters with healed catheter exit sites.

Intervention: Shower technique protocol and standard catheter care or control (standard catheter care only).

Analysis: Each measure of feasibility has its own statistical threshold for success. If the threshold is reached in 4 of the 5 measures, the full study will be deemed feasible.

Discussion: A pilot feasibility study of the larger study is critical due to the potential challenges associated with recruitment, compliance and participant ascertainment bias.

KEYWORDS: Hemodialysis; HIPPO-SAT; Shower technique protocol; Infections; Vascular Access; Catheter.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov

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INTRODUCTION

Background and Rationale

In North America, approximately 80% of incident and 20-50% of prevalent hemodialysis patients receive hemodialysis *via* a central venous catheter (catheter).[1,2] However, catheter use is associated with the highest morbidity and mortality of all vascular access types, primarily related to infection.[3-11] Catheter related bacteremia is the most clinically important type of catheter related infection due to their common occurrence and potential to progress to sepsis and death.[12] To prevent catheter related infection, patients should preserve the integrity and dryness of their catheter dressings.[13-16] Wet dressings place patients at increased risk of infection, especially if their catheter exit site is not fully healed. Thus, it has been recommended to avoid showering, as it is difficult to attain full protective coverage of the exit site using dressings and barriers.

Despite this recommendation, patients inevitably continue to shower. In a survey of 274 catheter dependent hemodialysis patients, 64% indicated that the recommended prohibition to shower was moderately to extremely inconvenient and reduced their quality of life. Additionally 77% of patients admitted to showering at least once while they had a catheter.[17] This is consistent with reports by hemodialysis nurses that patients often arrive to hemodialysis with wet and non-intact dressings due to showering.[18] In the USA, there are limited catheter shower covers available for patient purchase and are cost prohibitive (e.g. $6-8.00 USD/shower use) to the majority of the hemodialysis population.[2]

To address the desire of patients to shower yet respect the associated infection risk, we developed a shower technique protocol aimed to minimize the risk of bacterial entry at the catheter exit site for patients with a fully endothelialized catheter tunnel and healed exit site. This shower technique protocol was designed to enable patients to shower and change their dressing on average, 3 times per week.

OBJECTIVES

Our long-term goal is to determine whether a formalized shower technique protocol could simultaneously allow showering to improve patient satisfaction with catheter care yet not increase their risk of catheter related infection. However, prior to designing and implementing the needed rigorous clinical trial to answer this question, we sought to determine whether such a study is feasible, with the following objectives:

Primary Objective: To determine if it is feasible to conduct a large multi-centre randomized control trial in satellite hemodialysis patients dialyzing *via* a catheter to test whether the catheter related bacteremia rate is non inferior in patients who use the shower technique protocol and standard care compared to standard catheter care alone over 6 months. Feasibility is defined by 5 outcomes, each with its own statistical test and measure of success; 4 of 5 outcomes must be achieved for the full study to be feasible (Table 1).

Secondary Objectives: To validate both the Short Form-Vascular Access Questionnaire (SF-VAQ) and the catheter exit site healing tests.

The results of the HIPPO-SAT pilot study will also allow for estimation of sample size requirements for the following clinical objectives of the potential future study:

Primary future study objective: To determine the catheter related bacteremia rates when using 1) the shower technique protocol and standard care, and 2) standard catheter care alone in satellite hemodialysis patients with healed catheter exit sites over 6 months.

Secondary future study objectives: 1) To compare the change in patient satisfaction with their vascular access over six months (measured by the SF-VAQ), using the shower technique protocol and standard care *versus* standard catheter care alone, and 2) To capture the costs associated with the shower technique protocol and standard care.

METHODS

Study Setting

This feasibility pilot study will take place in the satellite hemodialysis units affiliated with 2 academic centres, the University Health Network-Toronto General Hospital (Toronto, On.) and London Health Sciences (London, On.), and 3 community centres, the Scarborough General Hospital (Toronto, On.), Trillium Health Centre- The Credit Valley Hospital (Mississauga, On.), and Mackenzie Health Hospital (Toronto, On.). All 5 centres are located in South Central Ontario, Canada.

Trial Design

This study will be a multi-centre, single-blinded, pragmatic, randomized feasibility study for a larger clinical trial of the same design.

Population: The study population will consist of individuals requiring chronic hemodialysis who have a tunneled catheter in situ for longer than six weeks who meet the study inclusion criteria.

Inclusion Criteria: 1. Informed written consent obtained (English speaking); 2. Age ≥18 years old; 3. Requires a tunneled catheter as their vascular access: a) End stage kidney disease without a functioning surgically created vascular access; b) End stage kidney disease whose peritoneal dialysis problems require transfer to hemodialysis for an anticipated prolonged period; 4. Passes 2/3 tests of catheter exit site healing (see below); 5. Must be

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Objective	Outcome Measure	Criteria for Success (Feasibility)	Method of Analysis
Primary Objective is the feasibility of the HIPPO-SAT study design defined by 5 outcomes below			
1. To assess the accuracy of capturing the catheter related bacteremia rate in the study within the satellite hemodialysis setting	The level of agreement between the date the nurse contacts the study coordinator to inform them of a suspected infection[a] and when the culture was sent to the lab	Kappa level >0.80	Kappa statistic
2. Determine the percentage of eligible hemodialysis patients who consent to participate	The percentage of consented eligible patients in each satellite unit	For each hemodialysis unit > 80%	Percentages and confidence intervals
3. Determine the percentage of satellite hemodialysis patients with catheters who are screened[b]	The percentage of satellite hemodialysis patients with catheters who are screened for eligibility	For each hemodialysis unit > 95%	Percentages and confidence intervals
4. Measure the success of shower technique protocol teaching	The percentage of patients in the intervention arm passing the Shower Technique Test at 3 and 6 months	>=80% of patients randomized to shower technique protocol	Percentages and confidence intervals
5. Determine the percentage of participants in the control arm who are using aspects of the intervention	The percentage of controls who are using aspects of the shower technique protocol which they were not using at baseline	<5% participants in the control arm	Percentages and confidence intervals
Secondary Objectives	**Outcome Measure**	**Criteria for Success OR Hypothesis**	**Method of Analysis**
Construct Validation of the Vascular Access Questionnaire (SF-VAQ)[c]	The change in SF-VAQ score over time using the shower technique protocol compared to standard care.	The shower technique protocol group will have a greater improvement in SF-VAQ scores than the control group over 6 months	Longitudinal regression model
Validation of the catheter exit site healing tests	The level agreement between the Deep Breath and Catheter Seal tests agree with the blinded photo test	Kappa level >0.80	Kappa statistic

[a]Catheter related infection will be defined by the Health Canada guidelines, and determined by the independent event adjudication committee Hemodialysis Infection Control Subcommittee using the "Suspected catheter related infection outcome reporting form" completed by the nurse at the time infection is suspected, the lab reports, and a detailed chart review following a suspected infection and related catheter removal, hospitalization, and death. The hemodialysis nurses must phone/inform the coordinator within 72 hours so that the "Suspected catheter related infection outcome reporting form" is completed promptly.
[b]Screening can be challenging as satellite units are remotely located as compared to in centre hemodialysis patients
[c]The Vascular Access Questionnaire is a measure of patient satisfaction with their vascular access that is previously not validated in this population

Table 1: Feasibility and Clinical Objectives for the HIPPO-SAT Pilot Study.

willing and able to take a shower as the standard form of body cleansing if randomized to receive the shower technique protocol; 6. Uses trisodium citrate (4%) as the standard catheter locking solution; 7. Their catheter has been in situ for ≥ 6 weeks.

Exclusion criteria: 1. Acute kidney failure, likely to be reversible with recovery of kidney function; 2. Non-tunneled catheter; 3. Antibiotic use by any route in the week prior to enrolling in the study, including intranasal mupirocin; 4. On immunosuppressant therapy; 5. Use of the catheter for purposes other than access for hemodialysis; 6. Involvement in another interventional study related to their vascular access; 7. Patient life expectancy <6 months (e.g. active malignancy; serious comorbidity such as hepatic failure); 8. Routine use of intraluminal thrombolytic (e.g. recombinant tissue plasminogen activator) or antibiotic as a locking solution; 9. Catheter insertion in a location other than the neck/chest region.

Interventions

The planned trial intervention in participants with healed catheter exit sites will be either: i) training and use of the shower technique protocol when the participant wishes to shower plus standard catheter care or ii) standard catheter care provided by hemodialysis nurses at the satellite centre (Figure 1). The duration of the intervention will be 6 months from the time of randomization. If a participating site uses a prophylactic barrier at the catheter exit site as part of their catheter care protocol, they may only apply Polysporin Triple Ointment as a topical prophylactic agent, as per guideline recommendations.[18] Patients will be taught to re-apply the Polysporin Triple Ointment according to standardized catheter care technique.

Shower Technique Protocol Details of the shower technique protocol will be published with the results of the HIPPO-SAT pilot trial to prevent problems with participant ascertainment bias. Participants will be given a minimum 30 minute personalized educational session by the study coordinator. They will be taught safe and clean techniques for showering with their catheter. Video and other educational materials for the shower technique protocol will be used to assist in training participants randomized to this intervention. The participant must successfully demonstrate the shower technique protocol on a training mannequin (Shower Technique Test) and be deemed by the study coordinator as ready to independently and correctly perform the shower technique protocol before proceeding. If the participant passes the Shower Technique Test, they will be provided a pamphlet on the shower technique protocol, not to be shared with

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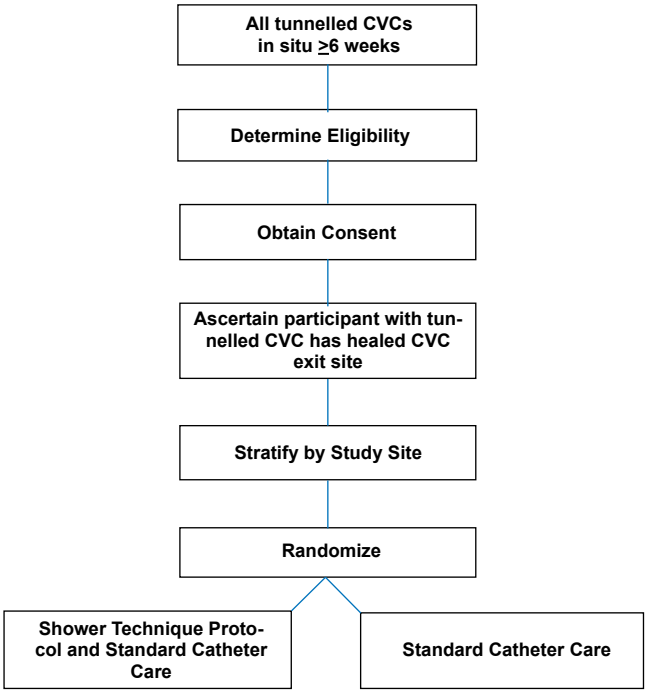

Figure 1: HIPPO-SAT Pilot Study Flow Diagram.

other participants, to be kept as a reference and placed in their bathroom/household. They will also be given the necessary supplies for the shower technique protocol, itemized in individual sequentially numbered kits, to take home. The study coordinator will track all these supplies for use in a separate cost analysis. Participants will be reassessed *via* the Shower Technique Test using the training mannequin 3 and 6 months following randomization.

Standard Catheter Care consists of cleansing with chlorhexidine 2% or povidone (if allergic to chlorhexidine) at the catheter exit site by trained hemodialysis nurses followed by placement of a dry gauze dressing by the hemodialysis nurse 1x/week or when clinically indicated. Nuanced differences may be present at participating units; however, the key components of the intervention are 1) hemodialysis nurse delivery of catheter care 2) chlorhexidine or povidone cleansing 3) dry dressing 4) standardized frequency. Study coordinators will check dialysis run sheets monthly to confirm that nurse administered dressing changes are compliant with standard catheter care; non-compliance will be documented and reported to the Principal Investigator, vascular access coordinator and local nephrologist.

Outcome Measures

HIPPO-SAT pilot study objectives and their corresponding outcome measures are listed in Table 1. The primary outcomes for feasibility will be evaluated at the screening, recruitment, and implementation phases of the study. The catheter care survey, a measure of participant's compliance and participant ascertainment bias with their catheter care protocol (also known as "study group treatment contamination"), and the SF-VAQ, a measure of vascular access specific satisfaction and quality of life, will be administered at baseline, 3 months, and 6 months post randomization.

The objective to assess the accuracy of the catheter related bacteremia rate capture in the satellite hemodialysis setting is critical for feasibility and will be described in detail. This will be measured by the level of agreement between the date the nurse contacts the coordinator to inform them of a suspected catheter related bacteremia and the date the culture was sent to the lab. The process for capturing the catheter related bacteremia rate is as follows: participants are clinically evaluated 3x/week on hemodialysis by their hemodialysis nurses, who are experienced at recognizing and managing patients with a suspected catheter related infection, including a catheter related bacteremia. The hemodialysis nurse will carefully inspect the participant's catheter exit site and surrounding area at each catheter exit site dressing change. At the first sign of infection the nurse will notify a provider (e.g. physician) and the study coordinator immediately, take the appropriate swabs and blood cultures to obtain organism growth and sensitivities. The study coordinator will complete a data collection form (see Appendix 1) for each suspected infection which includes the date the nurse contacts the coordinator and the date the culture was sent to the lab.

Participant Timeline

The planned recruitment period is 12 months and the total duration of follow-up will be 6 months (Table 2). Study visits will take place at baseline, 3 months, and 6 months post randomization. Baseline clinical, demographic, and vascular access information will be obtained from the chart and/or a short

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interview with the participant. The catheter care survey and the SF-VAQ will be administered to all participants at each study visit. For those participants allocated to the shower technique they will receive their education session at baseline, and be administered the Shower Technique Test at each study visit.

Sample Size

This pilot study will help determine the sample size and analysis plan for the potential future larger study. The current sample size considers 50% eligibility, 30% refusal, 10% non-compliance and <1% loss to follow-up. The estimates are based on the following infection rates: the rate of catheter related bacteremia achieved with Polysporin Triple Ointment is 0.26-0-.63/1000 catheter days, and the catheter related bacteremia rate using shower technique protocol based on preliminary data is 0.39-0.46/1000 catheter days.[18,19] This preliminary data is derived from an informal shower technique protocol that was used in 49 select patients with no prior catheter related infection and who had used the same catheter for 6 months. Using the HIPPO-SAT's broader inclusion criteria, the catheter related bacteremia rate may be higher. Data from each participating study site was also obtained to further support these estimates (data not shown). The planned recruitment target is 78 patients for the HIPPO-SAT pilot study.

Recruitment

The total study recruitment period will be 12 months from study initiation. Each study site will have 6 months to recruit participants; the study recruitment rate will be determined after the study recruitment period has ended. In order to protect against selection bias, all satellite hemodialysis patients with a catheter *in situ* for at least 6 weeks will be approached (see inclusion/exclusion criteria). A screening and recruitment log will be maintained and evaluated weekly during the recruitment period, to document reasons for exclusion and refusal.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation

Once written consent is obtained, the participant will undergo formal testing for catheter exit site healing. If any of the tests are failed, standard catheter care will continue; the patient can be reassessed weekly until recruitment ends. Randomization

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
TIMEPOINT**	*- (1-2) wk*	*0*	*1 wk*	*3 m*	*6 m*
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Catheter Exit Site Healing Test	X				
Allocation		X			
INTERVENTIONS:					
Education session at randomization on showering with catheter, changing dressing and applying Polysporin Triple Ointment at home (in addition to gold standard of care)		X	X	X	X
Shower Technique					
Control					
Standard of care Polysporin Triple Ointment applied at catheter exit site once per week					
ASSESSMENTS:					
Baseline characteristics, catheter exit site healing	X				
Continuous monitoring for signs of catheter related infection at least once per week at hemodialysis					
Catheter Care Survey monitoring compliance and contamination, SF-VAQ					
	X			X	X

Supplies for the shower technique protocol will be distributed to patients once monthly.

Table 2: Schedule of enrolment, interventions, and assessments.

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will occur immediately after the eligible participant from whom consent has been obtained meets the entry criteria of "healed catheter exit site".

Tests of Catheter Exit Site Healing

The tests of catheter exit site healing are as follows: **1) Deep Breath Stability Test** measures the migration of the catheter as marked by a 2 cm indicator on the catheter from the skin at the catheter exit (test passed if <3 mm movement between complete exhalation and inhalation); **2) Catheter Seal Test** is a visual inspection against an objective checklist to determine healing; and **3) Blinded Photo Test** where two photos are taken of the catheter exit site to be evaluated for healing by independent blinded trained assessors (test passed if both assessors agree that the exit site is healed). These catheter exit site healing tests will be repeated at least weekly, or when the exit site is exposed, until 2/3 criteria are met or recruitment ends. These tests are only used on catheters that are at least 6 weeks old to ensure that all catheter exit sites are fully healed prior to patients being randomized to the study intervention arms.

Participant retention

In order to enhance patient retention and reduce loss to follow up, study coordinators are all trained in Good Clinical Practice guidelines i.e. to ensure proper patient selection and consent. Participants may rescind consent from the study at any time (e.g., if they find the shower technique protocol too challenging). Loss to follow up should be minimal as hemodialysis patients represent a "captive" study population due to their dialysis needs.

Allocation concealment mechanism

The participants' necessary details will be provided to a 24-hour, telephone accessed independent central randomization desk (McMaster University) where each participant will be randomized and allocated to either the shower technique protocol and standard care or standard catheter care alone, and receive a corresponding unique study number. Allocation of patients to the intervention will be concealed to the randomization desk and will occur according to randomization sequence. The study coordinator will notify the participant of their allocation, and if randomized to the intervention arm, will immediately administer the shower technique protocol education session.

Sequence generation and implementation

Randomization will take place within strata formed by study site. The randomization schedule will be produced by a computer generated random number list, and will use a random permutated block design, with blocks sizes randomly selected. The central randomization facility (McMaster University) will know the randomization code. None of the study personnel or investigators will have direct access to the code.

Blinding

Patients and study coordinators cannot be blinded to allocation status due to the nature of the intervention; however, the outcome adjudication committee will be blinded to treatment allocation.

Statistical methods

The CONSORT criteria will be followed in the statistical analysis and reporting of this study. Study feasibility objectives, the corresponding measures of success and statistical tests are listed in Table 1. P-values < 0.05 will be considered statistically significant. All P-values will be two-sided and are unadjusted for multiple comparisons. All analyses will be based on an intention-to-treat approach. In sensitivity analyses, missing data will be imputed using multiple imputation methods. All analysis will use SAS v 9.4 and be carried out by a statistician blind to the intervention groups. There will be one analysis at the completion of this pilot study.

Monitoring of Trial Conduct and Procedures

To ensure conduct and reporting of the study that adheres to Good Clinical Practice, SPIRIT, and CONSORT guidelines, rigorous procedures have been put in place for the HIPPO-SAT pilot study. The procedures for data monitoring, obtaining and maintaining ethics board approval, protocol amendments are detailed below:

Data collection methods

All baseline and outcome data will be collected on paper data collection forms by the study coordinator, hemodialysis nurse, or Hemodialysis Infection Control Subcommittee member (Appendix 1 for example). They will then be entered into the computerized HIPPO-SAT pilot study database. There are no patient administered forms as the SF-VAQ and catheter care survey are both administered by the study coordinator to the patient.

Data management

All study data will be entered by the study coordinator into the HIPPO-SAT pilot study database. The HIPPO-SAT pilot study database is based on a Microsoft access platform and will be developed by a database developer and manager on the guidance of the study coordinator and the study statistician. It will be transferrable for analysis in the SAS (c) statistical program. A data dictionary will be created and maintained.

Data Safety Monitoring board and interim analysis

A Data Safety and Monitoring Board will not be re-

quired for this pilot study. However the study data will be continuously monitored for safety of the novel procedure. A Data Safety Monitoring Board will be assembled for the larger study, if this study is found to be feasible. There will be no interim analysis conducted in the pilot study.

Research ethics

Ethics board approval for this study has been obtained at the Scarborough Hospital, University Health Network - Toronto General Hospital, London Health Sciences Centre, Mackenzie Health Hospital, and at Trillium Health - The Credit Valley Hospital. In order to protect confidentiality before, during, and after the trial, personal information about potential and enrolled participants will be collected and maintained by the study coordinator at the study coordinating centre. The principal investigator, study coordinator, study statistician and monitors from the research ethics boards will be the only parties with access to the final dataset.

There are no relevant financial and other competing interests for principal investigators for the overall trial to disclose. The results of this study will disseminated at local, national, and international conferences and will be the final manuscript submitted to an indexed journal for publication. The local and principal investigators, as well as the trial steering committee will be included as authors in the final manuscript. No professional writers will be used to write the manuscript. (Appendix 2)

DISCUSSION

The inability to shower due to the potential increased risk for catheter related infection impacts on patients' satisfaction with the presence and use of their hemodialysis catheter. While preliminary experience with a shower technique is encouraging[18,20] it is critical to determine whether it is safe for use in patients with healed catheter exit sites (i.e. determine whether catheter related bacteremia rates using the shower technique protocol are not greater than with the gold standard of catheter care). It is also unknown whether using the shower technique protocol improves patient satisfaction with their catheter care. In non-randomized studies designed to answer these two important clinical questions there is a real potential for confounding as patients selected to use the shower technique protocol are likely to be those with minimal co morbidity, lowest infection risk, and highest level of compliance. Therefore it is critical that the new shower technique protocol be formally evaluated in a rigorously designed and implemented clinical trial prior to its widespread application.

However, prior to embarking on such a study, it is important to conduct a pilot study to address potential challenges associated with recruitment, consenting, catheter related bacteremia rate measurement, health care worker and patient compliance with the study interventions and protocol, and participant ascertainment bias in satellite centres. Each measure of feasibility in this pilot study tests whether these methodologic challenges are serious threats to the implementation of the potential future study. The most pressing concern that necessitates a pilot study are the issues of participant compliance and patient ascertainment bias (we refer to these as "study group treatment contamination").

In the control arm of the HIPPO-SAT pilot study patients will be educated on the importance of not showering with their catheter in order to improve compliance. A recently conducted survey at the Toronto General Hospital and Scarborough General Hospital found that patients were 3.8 times more likely to comply with the recommendation not to shower if they remember being told not to do so by a healthcare professional.[17] Patients randomized to the control arm will not be taught how to use the shower technique protocol, even if they admit to showering with their catheter. It is expected that a significant portion of patients in the control arm will shower against guideline recommendation, as per baseline; however, these patients are not considered crossovers as they are not using other aspects of the shower technique protocol, such as use of chlorhexidine swabs. As this is a pragmatic randomized trial design, *both compliant and non compliant patients will be included in this study in order to* reflect the clinical reality of hemodialysis patients in satellite units.

There is also potential for participant ascertainment bias in this study design where participants in the intervention arm share shower technique protocol techniques with the control arm participants. The control arm participants, however, will not have access to the training or necessary supplies required to properly perform the shower technique protocol -this will limit the impact of this bias. Where participant ascertainment bias exists, the extent of the problem will be measured in this pilot study. This is important for the external generalizability of the larger HIPPO-SAT study results because in non-study environments (i.e. clinical practice) there will be patients intermittently using the shower technique protocol within the same satellite unit. It is therefore necessary to understand the risks of participant ascertainment bias for those patients not using the shower technique protocol, which may be underestimated in the pilot study. Overall, the implication of this current pragmatic pilot design is to ensure future study feasibility and integrity while ensuring proper external validity and ultimately, greater practical generalizability to the real world setting.

CONCLUSION

The HIPPO-SAT Pilot study will determine whether a pragmatic randomized study design testing an educational intervention can be feasibly implemented in the satellite hemodialysis population. Statistical thresholds for capturing of the catheter related bacteremia rate, screening, recruitment, and shower technique education, as well as risk of participant ascertainment bias

must be adequately achieved for the study to be deemed feasible. The secondary objectives of this pilot design is to validate both the catheter exit site healing tests and the SF-VAQ. The latter importantly addresses the need to balance patient preferences and satisfaction with their catheter care with health care provider's concerns surrounding infection prophylaxis. With increasing patients with catheters in satellite hemodialysis, it is crucial that a pragmatic, yet effective, prophylactic catheter infection strategy be formally tested and established for this setting.

TRIAL SPONSOR: Kidney Foundation of Canada.

COORDINATING CENTRE: Toronto General Hospital is responsible for collection, management, analysis and interpretation of data.

TRIAL STEERING COMMITTEE: Lok C.E., Gafni A., Moist L., Thabane L.

ENDPOINT ADJUDICATION COMMITTEE: Batistella M., Bhola C.

COMPETING INTERESTS

In the past five years have no author on this manuscript received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future. None of the authors hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future. No author is declaring any patents relating to the content of the manuscript, or has received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript. No author has any other financial or non-financial competing interests competing interests to declare.

AUTHORS CONTRIBUTIONS

DK, CL, LM, and AG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. DK, CL, LT and AG participated in the design of the study and informed the statistical analysis approach. All authors read and approved the final manuscript.

AUTHORS INFORMATION

Dr. Charmaine Lok is director of the Renal Management Clinic and medical director of hemodialysis at the Toronto General Hospital. Dr. Lok is a Professor of Medicine at the University of Toronto and an Associate Professor in the Department of Clinical Epidemiology & Biostatistics at McMaster University.

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APPENDICES

Appendix 1

Criteria	Location		
	Catheter Exit site	Tunnel	Pocket site not contiguous with catheter exit site
Erythema	o Yes o No	o Yes o No	o Yes o No
Tenderness	o Yes o No	o Yes o No	o Yes o No
Induration	o Yes o No	o Yes o No	o Yes o No
Purulent discharge	o Yes o No	o Yes o No	o Yes o No
Positive culture of serous discharge or aspirate	o Yes o No If yes how many positive cultures:_____ If yes which organisms:_____ _____ _____ _____	o Yes o No If yes how many positive cultures:_____ If yes which organisms:_____ _____ _____ _____	o Yes o No If yes how many positive cultures:_____ If yes which organisms:_____ _____ _____ _____

- Was the blood culture positive for septic thrombophlebitis? o Yes o No
- Is there a greater than 10 fold colony count difference in blood cultures drawn from device and peripheral blood? o Yes o No
- Patient receiving immunosuppressive medication? o Yes o No
- Patient neutropenic? o Yes o No
- Patient receiving total parenteral nutrition? o Yes o No

Appendix 1: Suspected catheter Related Infection Form.

Appendix 2

Item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	8
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	8
	5b	Name and contact information for the trial sponsor	8
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	8
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-2
	6b	Explanation for choice of comparators	2
Objectives	7	Specific objectives or hypotheses	2,3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2

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Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	2
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	2-3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	3-4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	3,4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	3,4
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	3,4
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	3-5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6,7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	6,7

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Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6,7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6,7
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, *via* publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7
	31b	Authorship eligibility guidelines and any intended use of professional writers	7
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not included
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

SPIRIT 2013 Checklist*

Appendix 2: Spirit Guidelines.

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Review

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Individualized Sodium Prescription in Hemodialysis: An Ally for Better Dialysis Outcomes?

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ABSTRACT

The current practice in dialysis centres all over the world is to use standard sodium dialysate for all patients. Recently, there is a lot of interest in manipulating the dialysate sodium concentration to reduce fluid overload and achieve better cardiovascular outcomes. An ideal dialysate sodium concentration should provide intradialytic stability and abate the chronic volume and pressure overload that affects hemodialysis patients. Since the sodium set points in patients on hemodialysis is varied but individual specific, the focus is on individualized dialysate sodium prescription.

KEYWORDS: Hemodialysis, Sodium, Dialysis outcomes, Individualized dialysate.

ABBREVIATIONS: ECF: Extracellular fluid; IDWG: Interdialytic weight gain; LVH: Left Ventricular Hypertrophy; HD: Hemodialysis.

INTRODUCTION

Sodium is the most abundant cation in extracellular fluid and hence, the major determinant of serum osmolarity and Extracellular fluid (ECF) content. Hemodialysis patients are known to have a predialysis sodium level which is individual specific and different from sodium levels in a normal healthy individual.[1] Addition of extra sodium during hemodialysis influence Interdialytic weight gain (IDWG) and pre-dialysis blood pressure, which leads to higher volume and pressure overload, resulting in higher cardiovascular morbidity and mortality.[2-12]

RELATIONSHIP BETWEEN SODIUM AND FLUID BALANCE IN HEMODIALYSIS PATIENTS

In advanced renal failure, urea and other nitrogenous waste accumulation causes increased plasma osmolality. But urea is readily diffusable between cell membranes and hence is an ineffective osmole, i.e. it cannot establish an osmolality gradient. Thus, even in uremic patients, sodium is the predominant determinant of serum osmolarity and thus determines intracellular-intravascular fluid distribution, cell volumes, thirst and blood pressure.[13]

THE CONCEPT OF SODIUM SET POINT IN DIALYSIS PATIENTS

It has been consistently observed that HD patients have a constant predialysis plasma sodium concentration, and they also seem to have an individualized osmolar set point.[1,14] This value is highly conserved. Addition of extra sodium to the body will increase the thirst, thus increasing fluid intake so as to maintain the sodium and osmolar setpoints. De Paula studied 27 patients on hemodialysis and found that their pre-HD sodium levels were same irrespective

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of the dialysate sodium concentration which was used (standard Na+ HD, 134.0±1.4 mEq/L; individualized Na+ HD, 134.0±1.5 mEq/L; P= 0.735).[2] Table 1 shows the pre HD sodium values observed in various published studies.

SODIUM CONCENTRATION IN DIALYSATE

Dialysate is an artificial fluid which reconstitutes ECF by removal of urea and other waste products and transfer of electrolytes and water. In 1960's an 1970's, each dialysis session used to last 8-24 hours and contained low sodium levels of 126 mEq/L which removed 250-450 mEq salt ingested weekly.[15] With the advent of large surface area dialysers, dialysis became much more efficient and shorter. Use of hypotonic sodium solutions with the newer dialysers caused dialysis disequilibrium syndromes due to rapid reduction in plasma tonicity, characterised by nausea, vomiting, muscle cramps and hypotension. To combat this, between 1980 and 1995, dialysate sodium concentrations were progressively increased from 132 mEq/L to the current day 140-145 mEq/L.[13]

Use of high sodium dialysate (dialysate Na+ concentration higher than plasma) is not without its share of problems. Flanigan showed that over a 1 year period, dialysis patients have a relatively sodium setpoint which varied from 132 to 144 mEq/L in different patients and when these patients are dialysed with 140 mEq/L sodium dialysate, their pre-dialysis to post-dialysis sodium increased by 2.3-3.6 mEq/L. Since the body attempts to maintain the sodium setpoint, even if water is removed during dialysis, these patients will drink more water during interdialytic period causing excess weight gain, increased ECF volumes and thus, higher blood pressures.[13]

IMPORTANCE OF FLUID OVERLOAD IN HEMODIALYSIS PATIENTS

The most common cause of death in dialysis patients is cardiovascular cause, mostly due to lethal arrhythmia and the key condition associated with this is Left Ventricular Hypertrophy (LVH).[16-18] Left Ventricular Hypertrophy leads to activation of myocardial fibrosis pathways, which in turn leads to stiffened myocardium prone to dilated cardiomyopathy and aberrant conduction. Some studies have shown that regression in left ventricular mass occur with improvements in BP control and extracellular fluid volume.[19,20] As discussed earlier, sodium is the major determinant of extracellular volume. In dialysis patients, sodium is added to the body either *via* dietary intake or from dialysate. Hence, adjusting the dialysate sodium is an attractive measure to combat the dangers of LVH.

ALTERING THE HEMODIALYSIS SODIUM PRESCRIPTION FOR REDUCING SODIUM LOAD

An ideal dialysate sodium concentration should maintain sodium setpoint, optimize intradialytic stability and abate the chronic volume and pressure overload that affects hemodialysis patients. Too much of sodium in dialysate fluid can lead to complications as described above and too less can lead to intradialytic hypotension.[21,22] In hemodialysis patients, dialysate sodium minus pre-dialysis plasma sodium concentration (δDPNa+) and post-dialysis minus pre-dialysis plasma sodium (δPNa+) are taken as surrogates of sodium balance.

Sodium modeling programs are available on dialysis machines and allow alteration of sodium concentration over time. In eunatraemic dialysis, the diffusive sodium concentration gradient is neutralized to eliminate diffusive sodium fluxes. The diffusible sodium concentration is decided by several factors like plasma water sodium activity, charge characteristics, quantity of plasma proteins (Gibbs-Donnan effect), pH gradient across the dialyser membrane and sodium reflection coefficient of the dialysis membrane.[23] This will typically result in a 'eunatraemic' dialysate Na+ concentration of 1.5-5 mEq below the plasma concentration recorded by flame photometry or indirect potentiometry, which will cause no sodium loss or gain to blood.[23] Gibbs-Donnan effect in hemodialysis occurs due to nondiffusable, negatively charged plasma proteins which create an electric field that attracts sodium, thus reducing the diffusion of sodium from plasma across the dialysis membrane.[24] Hence, a correction factor of 0.95 (Donnan Coefficient) is applied to plasma sodium to get the dialysate sodium value which will result in eunatremic dialysis.[23]

CLINICAL EXPERIENCE WITH INDIVIDUALIZED SODIUM DIALYSATE

Several studies have shown that dialysate sodium prescriptions individualized to each patient's sodium set point can be beneficial (Table 1). De Paula et al. prospectively studied 27 hemodialysis patients in a single-blind crossover study. Subjects underwent nine consecutive HD sessions with the dialysate Na+ concentration set to 138 mEq/L (standard Na+ HD), followed by nine sessions wherein the dialysate Na+ was set to match the patients average pre-HD plasma Na+ measured three times during the standard Na+ phase multiplied by 0.95 (individualized dialysate Na+ HD). There was decrease in Interdialytic weight gain (IDWG), interdialytic thirst scores, and episodes of intradialytic hypotension in individualized Na+ phase compared with the standard phase.[25]

The results from other studies have been mostly similar. In an observational study with a facility level decrease in dialysate [Na+] from 141 mmol/l to 138 mmol/l, Thein et al. found no difference in IDWG but decrease in pre and post-dialysis systolic and diastolic BP, pre-dialysis plasma [Na+].[26] Aramreddy et al. reported on a case series of 13 patients undergoing thrice-weekly in-center hemodialysis with an individualized dialysate Na+ prescription in whom dialysate Na+ concentration was 2 mEq/L lower than average plasma Na+ over the preceding 3 months. Individualized dialysate Na+ was achieved in all patients through a stepwise weekly reduction of the standard dialysate Na+ prescription (140 mEq/L) by 2-3 mEq/L until reaching a

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Na+ gradient of -2 mEq/L (dialysate Na+ minus average plasma Na+ over the preceding 3 months).They found that individualized reduction of dialysate Na+ reduces IDWG without significantly increasing frequency of cramps or hypotension.[27] Similar results have been obtained by Elshahawy et al. who studied 40 stable chronic HD patients in a single-blind crossover design. Individualized dialysate Na+ concentration was associated with a decrease in IDWG and dialysis hypotension and related symptoms and better BP control in stable chronic HD patients.[28]

Individualizing sodium is found to be of benefit only in patients with sodium set point below the standard sodium in dialysate (usually 138-140 mEq/L). Kim et al. studied 19 patients on hemodialysis who were dialysed with individualized sodium concentration matching their serum sodium level. 13 of these patients had serum sodium higher than standard dialysate sodium. On implementation of sodium alignment, their thirst scores and interdialytic weight gain increased, with no effect on blood pressures or intradialytic complications.[29] Table 1 summarises the results from these studies on sodium modelling.

CONCLUSION

Dialysate sodium as a contributor to hypertension in patients on Hemodialysis (HD) has been unforeseen many a times. Recent data suggest that tailoring the dialysate sodium to individual's sodium setpoint has the potential for short and long term benefits for patients. Large scale randomized controlled trials are urgently required to convincingly prove the safety and efficacy of this very practical and easily implementable change in dialysis practice.

CONFLICTS OF INTEREST: None.

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Study group	Reference no.	Mean Pre HD Na+ level (mEq/L)	Intervention	Result
de Paula et al.	2	134	Compared standard dialysate phase (138 mEq/L) with individualized sodium phase (patients average pre-HD plasma Na+ measured three times during the standard Na+ phase multiplied by 0.95)	Decrease in interdialytic weight gain, interdialytic thirst scores, and episodes of intradialytic hypotension in the individualized Na+ period. Pre-HD BP was lower in individualized Na+ HD in patients with uncontrolled BP at baseline.
Thein et al.	26	139.7	Facility level decrease in dialysate [Na+] from 141 mmol/l to 138 mmol/l	Change in dialysate [Na^+] was associated with a statistically significant small to medium-sized decrease in pre- and post-dialysis systolic and diastolic BP, pre-dialysis plasma [Na^+], but not IDWG. Change was greatest in the patient tertile with the highest initial BP.
Aramreddy et al.	27	135.3	Individualized dialysate Na+ achieved in patients through a stepwise weekly reduction of the standard dialysate Na+ prescription (140 mEq/L) by 2-3 mEq/L until reaching a Na+ gradient of -2 mEq/L (dialysate Na+ minus average plasma Na+ over the preceding 3 months).	Decrease in IDWG% with no change in pre- or post-HD systolic or diastolic blood pressures, cramps, intradialytic hypotension.
Elshahawy Y et al.	28	137.45	Standard Na + (138mEq/L *versus* individualized Na+ (midweek pre-HD measured Na^+ by the Donnan coefficient of 0.95)	Lower IDWG, intradialytic hypotension, cramps and related, post-HD Na+ and better blood pressure control in individualized sodium group.
Jung ES et al.	29	140.1 in 'high sodium' group and 136.7 in 'equal sodium' group	Standard period (dialysis sodium concentrations were set at 136 (n= 15) or 138 mmol/L (n=4) *versus* individualized period (dialysate sodium levels aligned to individual serum sodium levels)	Increasing the dialysate sodium concentration based on serum sodium concentrations exacerbated weight gain and thirst in patients with negative sodium gradients.

Table 1: Clinical results of sodium modelling during hemodialysis.

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Case Report

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A Novel Case of Hypercalcemia Following the Use of Calcium Sulfate Beads

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CASE REPORT

In this case, we describe the first reported occurrence of severe, symptomatic hypercalcemia following the use of calcium based beads placed surgically into a hip arthroplasty.

The patient's consent for clinical history and x-rays has been obtained for the purposes of publication. A 72-year-old Caucasian female had an initial right Total Hip Arthroplasty (THA) on April 21st, 2014 (using an 11 mm high offset Taperloc Complete stem™, 50 mm Tri-Spike acetabulum™, 44 mm E-poly active articulation and 28 mm ceramic head) due to degenerative osteoarthritis, with operative findings of eburnated bone and severe arthofibrosis of the hip. On May 29th, 2014, she represented to the Emergency Room with severe pain in the right hip, redness along the surgical site; low grade fever (37.5 ºC) and mild leukocytosis (white blood cell (WBC) count 11 K/µL) with neutrophilia (82.8%). Initial blood cultures demonstrated no growth. She underwent a revision with a Biomet® 50 mm polyethylene Freedom acetabulum™, 36 mm head Freedom head™ with ultra-high dose antibiotic mixture. Intraoperatively, she was found to have purulent fluid throughout the hip and subsequently grew Methicillin-resistant *Staphylococcus aureus*. She had recurrence of severe pain in early August 2014 and was again readmitted on August 18th, 2014, found to have leukocytosis (WBC, 17.8 K/µL) where she underwent a second revision that involved the use of a 56 mm Regenerex acetabulum™ and 190 mm Arcos STS stem™, placed due to the previous stem. There was in duration, erythema but no obvious purulence during this procedure and subsequent cultures did not show evidence of growth. Three screws were placed for additional fixation. Antibiotic impregnated calcium sulfate beads (AICBs), using Osteoset™ beads, in this case with 2 g of Vancomycin and 3.6 g of Tobramycin, prepared by the hospital pharmacy department per company issued instructions, were implanted around and medial to the prosthesis and hip joint (Figure 1). Her post-operative course was initially complicated by Coombs positive hemolytic anemia, with a drop in hemoglobin to 4.7 g/dL for which she required several blood transfusions. Uncorrected Serum calcium levels began to increase on day 3 to 10.7 mg/dL. Calcium further increased through post-operative day 4 (13.3 mg/dL), at which time ionized calcium level was 7.55 mg/dL, peaked on day 5 (14.5 mg/dL) before decreasing, dropping to a normal level on post-operative day 8 (Figure 2). Immediate post-operative x-ray of the hip demonstrated the radio-opaque beads around and predominantly medial to the right hip where the beads were placed. To our surprise, the beads were no longer radio-opaque on the x-ray on post-operative day 5 (Figure 1), showing near complete-absorption. The patient exhibited symptoms of acute delirium, with an unsteady gait, and confusion. Her blood pressure had been controlled with systolic pressures consistently less than 140 mm Hg, increasing to a peak of 178/72 on post-operative day 6. She was unable to participate in physical therapy. Her past medical history included osteoarthritis, anxiety, and hypertension. Post-operative medications included vitamin D supplements at 1000 IU a day, acetaminophen, diphenhydramine, fluoxetine, ketorolac, gabapentin, folacin, cyanocobalamin, pyridoxine, pantoprazole and magnesium sulfate. Her physical examination was essentially unremarkable, with a clean healing surgical wound as the only pertinent finding. A full evaluation included vitamin D profile, Parathyroid (PTH) and PTH-related peptide levels and serum protein electrophoresis (Table 1), were unrevealing. We believe that the rapid absorption

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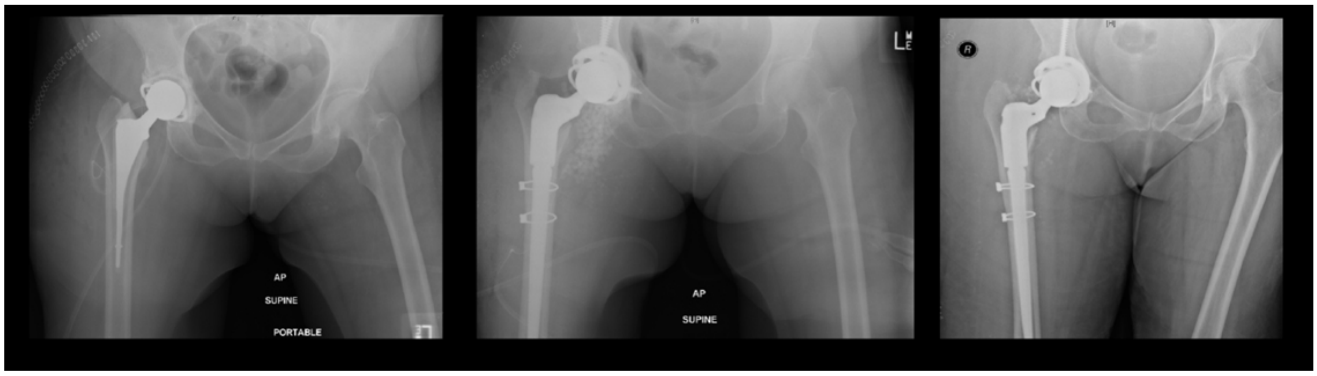

Figure 1: Series of Anteroposterior Supine X-rays, from left to right, initial film May 2014, immediately post-operatively (Aug 18th) and post-operative day 5.

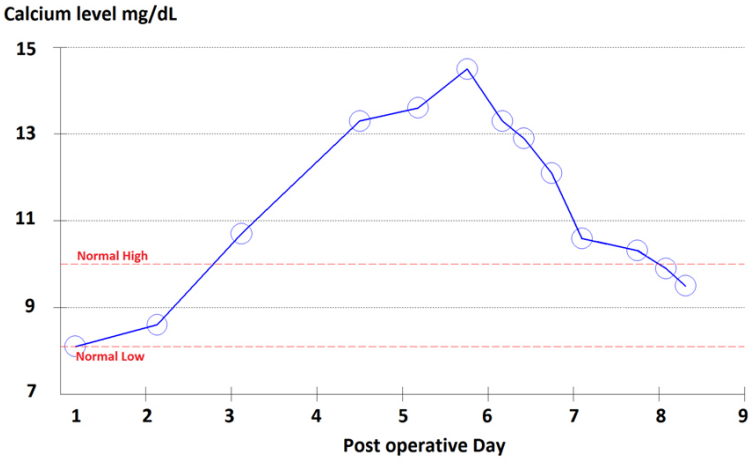

Figure 2: Calcium graph.

of the AICBs were responsible for the occurrence of hypercalcemia corresponding with calcium levels as seen on the graph (Figure 2). She had a minor renal injury apparent in June with a creatinine that increased to 2.12 mg/dL, however, at the time of readmission in August her creatinine had improved to 1.14 mg/dL, with minor fluctuation during this last hospital admission.

Lab	Value	Normal values
Total Uncorrected Calcium	13.6 mg/dL	8.1-10 mg/dL
25-OH-Vitamin D	26.4 ng/mL	30-100 ng/mL
1,25-OH-Vitamin D	13 pg/mL	15-75 pg/mL
SPEP	Negative	Negative
Intact-PTH	2.8 pg/mL	14-72 pg/mL
PTH-rP	4.3 pmol/L	0-3.4 pmolL
Mg	1.4 mg/dL	1.7-2.5 mg/dL
Creatinine Kinase	92 Units/L	20-155 Units/L
Phosphorous	2.1 mg/dL	2.3-4.4 mg/dL
Creatinine	1.16 mg/dL	0.5-1.2 mg/dL

Table 1: Laboratory values on post-operative day 5.

The patient was treated aggressively with intravenous saline, initially at a rate of 100 cc/hour and then increasing to 200 cc/hour during her highest blood calcium levels. Her hypertension was treated with amlodipine 10 mg orally daily. A single dose of calcitonin was administered of 200 IU/mL subcutaneously on post-operative day 7. Other treatment options were considered but felt inappropriate including further calcitonin dosing, bisphosphonates and loop diuretics. The patient right away responded to aggressive intravenous fluid therapy; and as the serum calcium improved, the confusion and delirium resolved. Ultimately, on post-operative day 9 she was transferred to a local rehabilitation unit. During follow visits she has done well without recurrence of pain in the hip or signs of infection.

DISCUSSION

To our knowledge, hypercalcemia has not been previously reported following the use of AICBs in any peri-prosthetic surgery. AICBs are being used more frequently in orthopedic surgery as they may act as both a bone graft substitute and provide a vehicle for local delivery of antibiotics. Methicillin-resistant *Staphylococcus aureus* (MRSA) dominates the infectious pathogens in post-operative orthopedic surgery, for which local delivery of antibiotics, such as Vancomycin, have the potential to significantly improve patient outcomes. Manufacturers of AICBs warn of possible transient hypercalcemia when using the product, however have not quantified this risk. Studies using AICBs in the past have shown absorption rates of ~93% at 1

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month and 100% at 3 months.[1] In contrast to these reports, x-rays taken on post-operative day 5 showed near complete absorption at the surgical site. Our x-rays, coupled with the dramatic rise in serum calcium, indicate an unambiguous correlation between hypercalcemia and the absorption of the AICBs, in the setting of an otherwise unremarkable serological evaluation. The patient developed an acute encephalopathy secondary to the hypercalcemia that prevented participation in standard post-operative physical therapy and presented a significant fall and aspiration risk.

It is unclear why the beads underwent such uncharacteristically rapid absorption in this case. Our team speculates that this may be due to the placement of the majority of the beads in adjacent vascular soft tissue, or a potential interaction between the antibiotics and the beads, that increased solubility. The dosing may have been liberal, although this in itself should not have affected the rate of absorption but rather the degree of hypercalcemia.

Recommendations for using AICBs in future cases include monitoring serum ionized calcium levels for the days following the procedure, in addition to pre- and post-operative tests for renal function**,** phosphate levels and post-operative evaluation hypercalcemic symptoms. In cases where the hypercalcemia cannot be ameliorated by fluids alone, other potential therapies such as loop diuretics or even hemodialysis may need to be considered.

Hip arthroplasty is a common surgical procedure, with an estimated 168,000 cases in individuals over the age of 65 in 2010.[2] By 2030, the number of procedures in the United States is projected to increase by 174% to nearly 600,000 procedures per year, while hip revision procedures are expected to double by the year 2026;[3] furthermore, MRSA infections in periprosthetic surgeries have had a historic occurrence of 1-2% in primary surgeries and rises to 3-4% in revision surgeries[1,4] and with the rise in the procedures the use of AICBs are also expected to increase. The combination of calcium beads with antibiotics is an off-label use and guidelines for AICBs are only specified for the use of the calcium beads alone. The mechanism of the rapid absorption of the calcium in our case is currently unknown, and we further recommend more studies on absorption rates of AICBs following the addition of antibiotics by manufacturers.

DECLARATIONS: None.

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