Protocol #: 19-1027
Project Title: Effect of Velphoro® on serum phosphate and albumin in peritoneal dialysis patients
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I. **Hypotheses and Specific Aims**: Disorders of mineral metabolism are common among patients with end stage kidney disease (ESKD). High serum phosphate levels are associated with an increased risk of death and cardiovascular disease in dialysis patients.[1-3] Hyperphosphatemia is a common problem in patients on peritoneal dialysis (PD).[4] Restricting phosphorus in the diet often leads to a decrease in protein intake. Decreased protein intake is associated with increased mortality in dialysis patients. Thus, diet alone is not effective in reducing phosphorus and improving protein intake in dialysis patients. Improving phosphate control and improving nutritional status may lead to improved outcomes in PD patients. Velphoro® (sucroferric oxyhydroxide)is an iron-based phosphate binder that is associated with less pill burden than other phosphate binders. In observational studies, the use of Velphoro® was associated with improved phosphate control, improved mineral metabolism and improved serum albumin in hemodialysis patients. In PD patients, there has only been 1 study performed that did suggest a trend towards improved nutritional status with the use of Velphoro®. However, this study was retrospective and used real world existing clinical data and had numerous limitations. Currently, no prospective studies have been performed to determine if Velphoro® improves nutritional status in PD patients. We hypothesize that improved mineral metabolism (improved phosphate, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23) control) with Velphoro® will allow for less dietary restrictions and will result in improved protein intake and higher serum albumin levels. Inflammation is also very common in patients with ESKD. Inflammation is a known factor that reduces serum albumin. Studies have found that disordered mineral metabolism is associated with inflammation in patients with ESKD. Hence, improving markers of mineral metabolism may also lower inflammation and lead to improved serum albumin. We are proposing a prospective pilot study to determine if changing the phosphate binder to Velphoro® for 6 months improves serum markers of mineral metabolism (phosphate, PTH, FGF23), serum albumin and nutrition status in PD patients. We will test the following aims:

Specific Aim 1: To determine the effect of Velphoro® on serum albumin, prealbumin, appetite and dietary restrictions in PD patients with low serum albumin.
Hypothesis: Velphoro® will result in an increase in serum albumin and prealbumin, an increase in appetite, and less dietary restrictions in PD patients with low serum albumin.

Specific Aim 2: To determine the effect of Velphoro® on serum markers of mineral metabolism (intact parathyroid hormone (iPTH), fibroblast growth factor 23 (FGF23), phosphate and calcium).
Hypothesis: Velphoro® will result in a decrease in serum phosphate, FGF23 and iPTH.

Specific Aim 3: To determine the effect of Velphoro® on serum markers of inflammation (C-reactive protein and IL-6).
Hypothesis: Velphoro® will result in a decrease in serum levels of CRP and IL-6.

II. **Background and Significance**:

Disorders of mineral metabolism are common among patients with end stage kidney disease (ESKD). High serum phosphate levels are associated with an increased risk of death and cardiovascular disease in dialysis patients.[1-3] Hyperphosphatemia is a common problem in patients on peritoneal dialysis (PD).[4] Dietary restriction of phosphorus is an important part of phosphate control. However, dietary restriction alone is not usually successful in controlling serum phosphate levels. Many foods that are high in phosphorus are high in protein, making balancing phosphorus and protein intake challenging. Hypoalbuminemia and malnutrition are associated with an increased risk of morbidity and mortality in dialysis patients.[5] Hypoalbuminemia is common in PD patients and is usually multifactorial in origin. Lower protein intake, loss of protein into effluent, decreased albumin synthesis, inflammation, etc. all play a role.[5] Peritoneal dialysis patients are prescribed high protein diets and often require dietary supplements. In some patients, despite these interventions, serum albumin remains low or continues to fall. Additionally, in some patients the high protein diet results in higher serum phosphate levels and the need for phosphate binders, contributing to pill burden. Inflammation is highly prevalent in PD patients.[5] Many observational studies have found that disordered mineral metabolism is associated with inflammation in patients with ESKD.[6,7] Hence, improving mineral metabolism may result in less inflammation and improve serum albumin.

Sucroferric oxyhydroxide is an iron-based chewable phosphate binder with a lower pill burden for treatment of hyperphosphatemia in both hemodialysis and PD patients.[8,9] In a retrospective study of 258 PD patients, Velphoro® resulted in 74% of patients achieving in-range serum phosphate levels after 6 months and decreased pill burden by 57%.[8] Interestingly, in hypoalbuminemic hemodialysis patients, serum albumin significantly increased with Velphoro® over a 12 month period from 3.4 g/dL to 3.7-3.8 g/dL.[10] In PD patients, a slight decrease was observed in albumin levels over 6 months, but to assess the impact of lowering serum phosphorus without further restricting dietary protein, serum albumin and the normalized protein catabolic rate were each divided by serum phosphorus.[8] An increase in phosphorus-attuned albumin and phosphorus attuned normalized protein catabolic rate were seen, suggesting that Velphoro® may improve nutrition status in PD patients.[8] This study was retrospective and used data from existing clinical records and missing data was an issue. The data relied on information from pharmacy fills of Velphoro®, reasons for patients changing to Velphoro® or off of the medication were not given, adverse events were not known and dietician nutritional advice was unknown. Additionally, the study did not examine markers of inflammation in PD patients.

The mechanism by which Velphoro® may improve nutrition status is unclear. Several mechanisms have been proposed. First, it is possible that improved phosphate/mineral metabolism control allows for less dietary restrictions leading to improved protein intake. Second, improved mineral metabolism may lead to less inflammation and improved serum albumin. Third, less pill burden, as is seen with Velphoro® compared to other binders, may lead to improved appetite and increased protein intake.

If a phosphate binder improves nutrition status in PD patients, this would have a significant impact on clinical practice. **Currently, no prospective studies have been performed to determine if** Velphoro® **improves albumin in PD patients.** We hypothesize that improved phosphate control will allow for less dietary restrictions and will result in improved protein intake. We are proposing a prospective pilot study to determine if changing the phosphate binder to Velphoro® for 6 months improves serum albumin and nutrition status in PD patients. Results from this study will be used to design and power a larger randomized trial.

III. **Preliminary Studies/Progress Report:** This is a pilot study so we do not have any preliminary data.

IV. Research Methods

Study design and population: A prospective, open-label pilot study of up to 50 patients on PD will be performed. Patients will be recruited from the Home Dialysis Clinic at the University of Colorado Anschutz Medical Campus (see inclusion/exclusion criteria below).

- Screening: Once subjects are identified as meeting criteria based on chart review, subjects will undergo screening for inclusion/exclusion criteria during a 1-2 week period. Demographics, medical history and physical examination will be performed.
- Baseline: During the baseline phase, demographics, medical history and physical examination, serum basic metabolic panels, iPTH, phosphate, calcium, FGF23, prealbumin, albumin, hs-CRP and IL-6 will be performed in all participants. Participants will complete the Appetite and Diet Assessment Tool (ADAT) and 3-day dietary history of nutrient intake. Participants will then be started on Velphoro® at the recommended starting dose of 1 tablet 3 times daily with meals and titrated by increments of 1 tablet until serum phosphate is < 5.5 mg/dL.
- Follow-up: Patients will come in for monthly visits as per standard of care.
    - Months 1, 2, 4 and 5: 1) Outcome measure: basic metabolic panel, phosphate, calcium, iPTH, albumin, self-reported ADAT, dietary changes/restrictions per dietician. 2) Adverse event assessment and compliance.
    - Months 3 and 6: In addition to the adverse event assessment, outcome measures: basic metabolic panel, phosphate, calcium, albumin, prealbumin, iPTH, FGF23, hs-CRP and IL-6, self-reported ADAT, 3-day dietary history of nutrient intake, any dietary restrictions/changes will be recorded.

2) **Study Drug Dosing:** The Velphoro® will be provided by Fresenius Medical Care Renal Therapies group.

- Washout period: All patients previously on a phosphate binder will wash out for 2 weeks.
- Initial starting dose: After the washout period, patients will be started on 1 tablet 3 times daily with meals, which is the recommended starting dose of Velphoro®.
- Monthly titration: Serum phosphate levels will be monitored monthly and Velphoro® will be titrated in increments of 500mg (1 tablet) per day until serum phosphate is <5.5 mg/dL.

a. Sample size

This is a pilot study and the results from the pilot study will be used to power a larger, randomized trial.

b. Patient population and inclusion and exclusion criteria

After obtaining their written informed consent, up to 50 patients on peritoneal dialysis will serve as subjects. Men and women 18 years and older of all races/ethnicities will be included. Major inclusion/exclusion criteria are presented in the table below. Patients will be recruited from the Home Dialysis Clinic at the University of Colorado Anschutz Medical campus.

Inclusion Criteria	Exclusion Criteria
• Age ≥ 18 years • On peritoneal dialysis at least 3 months with a Kt/V of ≥ 1.7 • Use of Automated Peritoneal Dialysis • Serum phosphate ≥ 5.5 mg/dL or ≤5.5 mg/dL on a binder other than Velphoro® • Serum albumin ≤ 3.8 g/dL • Able to provide consent • Ability to complete self-reported questionnaire	• Inadequate dialysis • Current use of Velphoro® • Significant comorbid conditions that lead the investigator to conclude that life expectancy is less than 6 months • Active malignancy • Recent episode of peritonitis • Pregnancy or planning to become pregnant • Anticipated kidney transplantation within 6 months • Factors judged to limit adherence to interventions • Known adverse side effect to Velphoro®

Outcomes: Serum phosphate and serum albumin are the main outcomes of the study. Secondary outcomes include other markers of mineral metabolism, FGF23, PTH and inflammatory markers (IL-6 and CRP).

Justification for endpoints:

- Serum albumin level has been an indicator of nutrition status in PD patients and is associated with increase mortality.[5] Additionally, serum albumin levels are routinely drawn (monthly) in PD patients and is a quality measure that is reported for nutrition status. Prealbumin levels are an independent and sensitive predictor for mortality in PD patients.[11] Prealbumin is a more sensitive marker for protein-energy malnutrition than albumin.[12]
- To assess appetite, participants will complete the Appetite and Diet Assessment Tool (ADAT) and 3-day dietary history of nutrient intake. The ADAT is a validated tool that has been used in dialysis patients. Additionally, a registered dietician will meet with the patient monthly and any changes in dietary restrictions will be recorded.
- Markers of mineral metabolism include phosphate, calcium, PTH and FGF23. Hence, we will measure all of these markers in order to determine the overall changes in mineral metabolism. In studies examining disordered mineral metabolism, it is standard to measure all of these markers.
- Inflammatory markers that have been shown to be elevated in PD patients include C-reactive protein and Interleukin-6. These are common surrogate markers used to measure inflammatory burden and have been shown to predict adverse outcomes in PD patients.[13]

Potential Scientific Problems:

- Although subject recruitment and retention are always challenging, we should be able to complete the study in the proposed timeline given our groups excellent track record in recruiting and enrolling participants in clinical trials. The PI completed a randomized clinical trial of 128 patients with CKD stage 3B-4 and all patients were enrolled within 3 years (K23 DK087859).
- We should have few difficulties with the proposed procedures and protocols as they involve only laboratory measurements and questionnaires during the patients routine monthly visit.
- We recognize that different phosphate binders exist. We chose Velphoro® as the studies are consistent in showing that it has a lower pill burden than other phosphate binders and is more effective.
- We recognize that Velphoro® may be titrated more frequently than monthly to obtain serum phosphate at goal of <5.5 mg/dL. We chose monthly titration as this is standard of care in dialysis patients and would not require additional patient study visits to lessen participant burden.

Statistical Considerations:

This is a pilot study to collect preliminary data and the sample size of 20 patients has been determined based on availability and feasibility, not on pre-specified statistical power. The paired t-test is applicable to examine the change from baseline to month 6 and is the basis of the following power analysis for simplicity. With a two-sided type I error rate of 0.05, 20 patients will provide a power of 82% if the effect size is 0.70. The power will be 91% if the effect size is 0.80. We propose to analyze the data using mixed effects model and the power could be higher. We have added this to the protocol.

Descriptive statistics of baseline characteristics and outcome variables will be provided for all enrolled participants; mean and standard deviation for continuous variable and

proportion for categorical variable. To examine how each of the outcome variables change over time, we will first provide longitudinal plots to examine the trajectories of outcome measures across time. This will give us an insight into the data and help in the selection of statistical model in the further analysis. Then longitudinal data analysis with mixed effects model will be performed with adjustment for age, sex, and other important covariates. The longitudinal plots will help in selecting an initial appropriate model and model diagnosis will be performed to finalize the analysis. A two-tailed P-value <0.05 is considered statistically significant. All analyses will be performed using SAS 9.4 or higher (SAS Institute, Cary, NC).

Data management: Study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes University of Colorado–Denver and was initiated at Vanderbilt University. Currently 52 institutions in 4 countries are using the software. The database is hosted at the University of Colorado–Denver Development and Informatics Service Center (DISC), which will be used as a central location for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the DISC. This iterative development and testing process results in a well-planned data collection strategy for individual studies. Both REDCap and REDCap Survey systems provide secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. These systems offer easy data manipulation with audit trails and reporting for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). Both systems were found to meet or exceed all of the security audit requirements.

Summarize Knowledge to be Gained: If successful, the results from this study will be used to power a larger randomized trial in PD patients. The ability to improve both phosphate control and nutrition status in PD patients could have a major impact on the field.

Protection of Human Subjects:

Potential Risks: There are no psychological, social or legal risks beyond those of participation in health-related research in general. The risk is greater than minimal to patients as they will be given drug therapy with Velphoro®. As with any medication there is a small chance of an allergic reaction. The main side effect of this medication is discolored feces and diarrhea. The majority of diarrhea events are mild and transient.

Risk of receiving sucroferric oxyhydroxide (Velphoro®) : This medication is well tolerated. The most common side effect reported is discolored stool (dark). This is due to the iron in the medication. This effect is harmless. Other common side effects include nausea and diarrhea. The majority of diarrhea events are mild and transient, occurring soon after start of treatment. This is included in the informed consent.

Risks of Having Blood Taken: In this study we will need to collect about one-half cup of blood from you. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You will not be getting extra blood draws during the study beyond the standard of care. We will be taking extra tubes of blood from you.

- Common side effects: You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.
- Rare side effects: There is also a small chance that you could feel lightheaded or faint during the blood draw.

Plan to minimize risk: The potential general risks of the proposed studies will be minimized by: 1) screening for adverse events and allergies to drugs; 2) constant personal monitoring of each experimental session by the investigators; 3) the appropriate clinical supervision, availability of emergency equipment and medications and the overall safety provided by the research environment; 4)the complete confidentiality of the record keeping process to be employed. All subjects identities and records will remain strictly confidential. Individual subject data will not be associated with subject name. The PI, Dr. Kendrick will be responsible for monitoring the study and adverse events and reporting them to COMIRB and the study sponsor.

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