The effects of oral vitamin D supplementation on the prevention of peritoneal dialysis-related peritonitis: study protocol for a randomized controlled clinical trial

**CURRENT STATUS:** ACCEPTED

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**DOI:**  
10.21203/rs.2.12622/v1

**SUBJECT AREAS**  
Internal Medicine  
Integrative & Complementary Medicine

**KEYWORDS**  
Natural Vitamin D3, Peritoneal dialysis, Peritonitis, Serum 25(OH)D, Randomized Controlled Trail
Abstract
Background: Vitamin D deficiency has been shown to be closely associated with peritoneal dialysis (PD)-related peritonitis. The aim of this study is to examine the feasibility of conducting a large, powered randomized controlled trial to determine the effects of vitamin D supplementation on the risk of PD-related peritonitis in patients who have already experienced an episode of peritonitis.
Methods: This prospective, open-label randomized controlled pilot trial with blinded end-points (PROBE) aims to determine the feasibility of oral vitamin D supplementation and to explore its effects on the risk of subsequent PD-related peritonitis among PD patients who have recovered from a recent episode of peritonitis. Eligible patients will be randomized 1:1 to either oral vitamin D supplementation (2000 IU per day; intervention group) or no vitamin D supplementation (control group) in addition to usual care according to International Society for Peritoneal Dialysis (ISPD) Guidelines. The sample size will be 30 for both groups. All participants will be followed for 12 months. The primary outcome is the assessment of feasibility (recruitment success, retention, adherence, safety) and fidelity (change in serum 25-hydroxy vitamin D level during follow-up) for a large, powered randomized controlled trial to determine the effects of vitamin D on the risk of PD-related peritonitis in the future. Secondary outcomes include time to peritonitis occurrence, recovery of peritonitis, peritonitis-related transition to hemodialysis, and peritonitis-related death (defined as death within 30 days of peritonitis onset). Discussion: This is the first randomized controlled trial investigating the effects of vitamin D supplementation on the risk of subsequent PD-related peritonitis among patients on PD. The findings for this pilot study will determine the feasibility of conducting a full-scale randomized controlled trial, which may provide a new strategy for preventing PD-related peritonitis among PD patients. Trial registration: Clinicaltrails.gov, NCT03264625, registered on 29 August 2017. https://www.clinicaltrials.gov/ct2/show/NCT03264625?term=NCT 03264625&rank=1, assessed on 1 July 2019.
Background
Peritoneal dialysis-related peritonitis (PD-related peritonitis) is the most common infectious complication for patients on PD, and is a major contributor to treatment failure, hospitalization and
Indeed, PD-related infection is considered to be the top, most critical research priority in PD by patients, caregivers and clinicians ([2, 3]). Almost 40% of patients will experience one or more episodes of peritonitis during extended follow-up on PD.[4] Furthermore, once patients experience an initial peritonitis episode, they are at increased risk of a subsequent, more serious peritonitis event after a median time interval of eight months.[5, 6] Key risk factors for the development of peritonitis include innate and adaptive immune dysfunction, inflammation and malnutrition [7-10]. Vitamin D deficiency is commonly associated with malnutrition [6] and is observed in the majority of dialysis patients [11, 12]. In addition to playing a role in the regulation of both the innate and adaptive immune systems [13, 14], vitamin D deficiency has been found to be independently predictive of increased risks of a variety of infectious diseases in the general population.[15-17] Previous observational cohort studies have also reported that vitamin D deficiency is associated with an increased risk of PD-related peritonitis, even after adjusting for comorbidities, nutritional status and physical performance.[6] Interventional studies also demonstrated that oral supplementation of vitamin D may reduce respiratory infection rates. [18, 19]

Therefore, we plan to conduct a pilot study to examine the feasibility for a future, full-scale randomized controlled trial (RCT) exploring the effect of oral vitamin D (Liquid natural vitamin D3, Cholecalciferol; 2000IU; 0.08mL) on the risk of PD-related peritonitis in patients who have already experienced an episode of peritonitis. Our hypothesis is that oral supplementation of vitamin D could reduce the risk of subsequent peritonitis.

**Methods**

**Trail design and setting**

This is a pilot, single-center, randomized, open-label, controlled trial with balanced randomization (1:1) among patients on PD. The protocol of this study was reported adhering to the ‘Standard Protocol Items: Recommendations for Interventional Trials’ statement.[20] After informed consent, all eligible participants will be randomized to the intervention group with vitamin D supplementation or control group. Participants will be followed for 12 months. **Figure 1** shows the schema of the trial. The study is being conducted in the PD center of Peking University First Hospital.
Ethical approval, trial registration, and dissemination

The study was approved by the Peking University First Hospital Research Ethics Committee (Project-ID:2016[1149]), and was registered at Clinicaltrials.gov[21] on 29 August 2017 (Registration number: NCT03264625[22]). The results will be disseminated in peer reviewed journals, lay summaries will be presented on “ScienceOpen”[23].

Study population

All patients who have recovered from a PD-related peritonitis at one month after the episode will be screened for eligibility. Patients will be recruited if they meet all of the following criteria: age at least 18 years; undergoing PD ≥1 month and clinically stable; weekly Kt/V ≥ 1.5 and no clinical uremic symptoms; and, serum 25-hydroxy-vitamin D [25(OH)D] <75nmol/l (30ng/ml). Patients will be excluded if they have any of the following: received vitamin D2/D3 or drugs known to alter serum 25(OH)D levels during the previous 12 months; have history of allergic reaction to cholecalciferol; have current or past malignant disease, active hepatitis or hepatic failure, acute systemic infection, active autoimmune diseases, severe digestive malabsorption or eating disorder, human immunodeficiency virus infection or acquired immune deficiency syndrome (HIV/AIDS); have a high probability (assessed by the recruiting physician) of receiving a kidney transplant or transition to hemodialysis (HD) or drop-out due to socioeconomic causes within 6 months; or women who were pregnant or lactating.

Written informed consent will be required from all study participants before their involvement in the trial. Participants can choose to withdraw from the study at any time without affecting their future treatment. Reasons for non-inclusion and withdrawal will be recorded in detail.

Randomization and blinding

All consenting patients will be registered in the trial and randomized 1:1 to either the vitamin D intervention group or the control group by a computer-generated random number list. An independent medical staff is responsible for participant enrollment and allocation assignment. The sample size for this pilot study will be 30 for both groups. (Fig 1) Due to the nature of medication intervention, neither participants nor researchers can be blinded. However, both the primary outcome
(the occurrence of a subsequent peritonitis) and the key secondary outcome (the short-term outcome of subsequent peritonitis) will be evaluated by independent medical staff who are blinded to participants’ allocations. In addition, all laboratory parameters for all participants will be measured by laboratory staff who are also blinded to treatment assignment.

**Intervention**

Participants in the intervention group will receive additional vitamin D (Liquid natural vitamin D3, Cholecalciferol; 2000IU) in a dose of 0.08mL orally per day for 12 months following randomization. In order to assess medication adherence, participants will be asked to take the study medication that is left over for weighing on each clinical visit.

**Control**

Participants in the control group will not receive any study drug and will be asked to not take any form of vitamin D supplementation.

**Concomitant treatment**

For both the intervention and control groups, all dialysis and other medication prescriptions will be in accordance with routine clinical care and International Society for Peritoneal Dialysis (ISPD) guideline recommendations.

**Baseline evaluation and follow-up**

Data collection for this study is composed of two phases: baseline evaluation and follow-up. All the data will be recorded by the responsible physician in a uniform case report form (CRF). Detailed information collected in each phase is described below. **Table 1** shows an overview of data collection schedule during baseline evaluation and follow-up. All participant information will be collected and maintained by trained medical staff to protect confidentiality.

**Baseline evaluation**

For all eligible and consenting patients, information regarding demographic data (age, gender, body mass index [BMI], education, marital status, occupation, income, health insurance), dialysis duration, primary disease, co-morbidities, current medication, and history of PD-related peritonitis will be recorded. Baseline biochemistry indices (including blood routine, serum creatinine, albumin, alanine
transaminase, electrolytes and serum 25(OH)D levels), dialysis adequacy (including urea clearance index [Kt/V] and creatinine clearance rate [Ccr]) and inflammatory biomarkers (interleukin-6, plasminogen activator inhibitor-1) will be evaluated. After randomization, the assigned treatment should be recorded in detail.

**Follow-up and Outcomes Evaluation**

All participants are planned to be followed-up for 12 months, with clinic visits every month. During the follow-up, clinical information including self-reported symptoms, and physical examination will be gathered. Biochemistry indices (including serum 25(OH)D level) and dialysis adequacy will be evaluated every three months. Participants will be evaluated for compliance by weighing residual liquid vitamin D3 every month. All outcomes and adverse events will be recorded. Please refer to the following sections for detailed outcomes and adverse events.

The primary outcome is assessment of feasibility (recruitment success, retention of participants for 12 months, patient adherence, and safety), and fidelity (change in serum 25(OH)D level between baseline and 12 months). Secondary outcomes include time to peritonitis occurrence, recovery of peritonitis, peritonitis-related transition to HD, and peritonitis-related death (defined as death within 30 days of peritonitis onset). Death not associated with peritonitis, transition to HD not associated with peritonitis, and receiving a kidney transplant will be recorded as competing outcomes.

Recruitment success will be measured through participant recruitment per month. Reasons for non-participation from those who are eligible to participate but refuse will be recorded. Retention will be evaluated by measuring attrition during the follow-up at each clinic visit. Adherence of taking vitamin D will be evaluated by weighing of vitamin D that is left over on each clinical visit.

For the assessment of safety, both severe and non-severe pre-specified adverse events (AE) during the study course, including allergic reaction to vitamin D, hypercalcemia, and hyperphosphatemia, will be recorded. Severe adverse events (SAE) include AE which fulfils at least one of the followings: life-threatening, requires hospitalization, results in disability or congenital abnormality, requires medical intervention to prevent one of the above outcomes.

The recovery of peritonitis was defined as complete resolution of peritonitis (normalization of body
temperature, resolution of abdominal pain, clearing of dialysate, and PD effluent white blood cell count $\geq 100$ cells/µL with $\geq 50\%$ polymorphonuclear cells by using antibiotics alone without relapse within 4 weeks of completion of therapy).

**Biochemical testing methods**

Blood samples will be analyzed at Peking University First Hospital, Beijing. Biochemical profiles will be tested using an automatic Hitachi chemistry analyzer. Serum 25(OH)D levels will be measured using an electrochemiluminescence method (Roche Diagnostics, E601, Germany).

**Statistical analysis**

Statistical analysis will be conducted using SPSS (version 22.0, SPSS Inc.) and SAS software (version 9.4, SAS Institute). Continuous variables will be expressed as mean ± standard deviation, median with interquartile range, and percentages. Student’s t-test, Mann-Whitney U test, and the Chi-square test will be used to compare differences in baseline characteristics between intervention and control groups.

Recruitment success, retention rate, adherence rate, and AE will be reported as percentages.

Competing risks Cox regression models will be used to compare time to peritonitis between the two groups. Logistic regression models will be applied to compare the short-term outcome of subsequent peritonitis. Linear mixed-effects regression models will be used to analyze the change in serum 25(OH)D levels between two groups.

For all statistical analysis, the level of significance will be set at 0.05.

**Patient and Public Involvement**

PD-related peritonitis is the most common infectious complication for patients on PD. Indeed, PD-related infection is considered as the most critical research priority in PD by patients, caregivers and clinicians. Patients will be involved in the recruitment and conduction of the present trial. The results will be disseminated to study participants by presenting on “ScienceOpen”[23]. The burden of intervention will be assessed by patients themselves though questionnaires.

**Discussion**

The present pilot RCT aims to evaluate the feasibility of oral vitamin D supplementation among PD
patients and to explore its effects on the risk of PD-related peritonitis. Few interventional study has been done exploring the effects of vitamin D on preventing infection, especially among PD patients. Therefore, obtaining data on evaluation of feasibility is the priority in this study. The findings of this pilot study will be used to inform the design and methodology of a definitive study evaluating the efficacy and safety of vitamin D supplementation in the prevention of PD-related peritonitis among patients on PD.

In the general population, there are many RCTs exploring the effects of vitamin D in preventing infections, such as respiratory infections in vitamin D deficient patients with chronic obstructive pulmonary disease [24], and children.[18] However, no such study has been undertaken in patients with end-stage kidney disease even though vitamin D deficiency has been shown to be independently associated with PD-related peritonitis [6].

Our study has applied a rigorous design in choosing the time-point for patient enrollment. According to previous cohort studies, patients having experienced a peritonitis episode tend to develop a subsequent one after a median time interval of eight months.[5] Therefore, we focused our attention on the prevention of a subsequent peritonitis episode during a 12 month period among PD patients who have recently recovered from peritonitis, given that this is expected to provide an enriched cohort of patients with a high peritonitis event rate. Based on current data, more than 20% of participants have developed one or more subsequent episodes of peritonitis during a one-year observation period. As ISPD guidelines recommend a standardized treatment period of 2-3 weeks for PD-related peritonitis, [25] we chose to enroll patients into the present study one month after the onset of a PD-related peritonitis, as antibiotic treatment would be expected to completed by this time.

According to the US Dietary Guidelines, the recommended daily dose of vitamin D for older adults is 600-800 IU per day.[26] while a meta-analysis of randomized controlled trails in the general population showed a usual dose of 300-2000 IU per day.[27] In non-dialysis CKD patients, a systemic review indicated that at least 2000 IU Vitamin D per day is necessary for ameliorating Vitamin D deficiency.[28] In dialysis patients, a randomized controlled trial among maintenance hemodialysis patients showed that a weekly dose of 10,333 IU cholecalciferol for 15 weeks could raise vitamin D
levels from 13.3ng/mL to 23.6ng/mL.[29] Participants in all of these studies showed an improvement in serum 25(OH)D level, with low incidences of hypercalcemia and hyperphosphatemia. As participants in our study need to take vitamin D for a whole year, after considering security, efficacy and feasibility, we chose to set the dose of vitamin D at 2000 IU. The liquid form of vitamin D was chosen for the sake of convenience in oral administration and evaluation of compliance. Vitamin D deficiency has been identified as one of the common modifiable risk factors for PD-related peritonitis.[30] Exploring whether supplementation of vitamin D could lower the risk of subsequent peritonitis would help identification of a potentially novel and cheap strategy for preventing PD-related peritonitis. Furthermore, the role of vitamin D supplementation on outcomes of PD-related peritonitis will also be explored. The result of this pilot study will determine the feasibility of conducting a full-scale RCT, which may help to better inform shared decision-making by patients and clinicians with respect to the role of vitamin D supplementation regarding the prevention and mitigation of PD-related peritonitis.

**TRIAL STATUS**

This is the first edition of protocol [Date:2016.9.30] approved by the ethics committee of Peking University First Hospital. The first participant was enrolled on 30 September 2017. Currently, 42 patients have been recruited into the study and the final recruitment target is 60. Recruitment and follow-up are scheduled to continue until 30 January 2021.

**Abbreviations**

PD: peritoneal dialysis; PROBE: prospective, open-label randomized controlled pilot trial with blinded end-points; IU: international unit; ISPD: International Society for Peritoneal Dialysis; 25(OH)D: 25-hydroxy-vitamin D; RCT: randomized controlled trial

**Declarations**

**Ethics approval and consent to participate**

The study is approved by the Peking University First Hospital Research Ethics Committee. (Project-ID:2016[1149]) Written informed consent is required from all study participants before their
involvement in the trial.

Consent for publication

Not Applicable.

Availability of data and material

The datasets generated during the current study are not publicly available due to the issue of individual privacy, but are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflict of interest to declare.

Funding

This trial was conducted with no external funding, no internal funding, or any grants.

Author contributions

Research idea and study design: JD, YZ, HP, DJ; data acquisition: XX, YZ, ZKY, ZQ, YX; data analysis plans: YZ, JD; supervision or mentorship: JD. Each author has contributed important intellectual content to the conception and design of this study. All authors were involved in drafting the manuscript or revising it, and accept accountability for the overall work by ensuring that questions on the accuracy or integrity of any portion of the work are appropriately resolved. All authors have given final approval of the version to be published.

Acknowledgements

The authors express their appreciation to the patients, doctors, and nursing staff of the Peritoneal Dialysis Center of Peking University First Hospital.

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Table 1

Table 1 Data collection schedule

Abbreviation: PMH: past medical history

Figures
| Demographic data, PMH and medications | Baseline | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 44 | Week 48 |
|---------------------------------------|----------|--------|--------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Clinical symptoms and adverse events  | X        | X      | X      | X       | X       | X       | X       | X       | X       | X       | X       | X       | X       |
| Biochemical indices                   |          |        |        |         |         |         |         |         |         |         |         |         |         |
| Blood routine                         | X        | X      | X      | X       | X       | X       |         |         |         |         |         |         |         |
| Blood biochemistry                    | X        | X      | X      | X       | X       | X       |         |         |         |         |         |         |         |
| Serum 25(OH)D                         | X        | X      | X      | X       | X       | X       |         |         |         |         |         |         |         |
| Dialysis adequacy                     |          |        |        |         |         |         |         |         |         |         |         |         |         |
| Weekly Kt/V                            | X        | X      | X      | X       | X       | X       |         |         |         |         |         |         |         |
| Weekly Ccr                            | X        | X      | X      | X       | X       | X       |         |         |         |         |         |         |         |
| Adherence                             |          |        |        |         |         |         |         |         |         |         |         |         |         |
| 24hr recall                           | X        | X      | X      | X       | X       | X       | X       | X       | X       | X       | X       | X       | X       |
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