Vitamin C Supplementation Intervention for Patients with Heart Failure—A Pilot Study

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Protocol Title: **Vitamin C Supplementation Intervention for Patients with Heart Failure—A pilot study**

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Date: 4/21/2020

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Abbreviations and Definitions of Terms

Abbreviation	Definition
HF	Heart failure
HRQOL	health related quality of life
RCT	Randomized controlled trial
G6PD	glucose-6-phosphate dehydrogenase deficiency
UNCH	University of North Carolina at Chapel Hill Hospital
MLHFQ	Minnesota Living with Heart Failure questionnaire
MSAS-HF	Memorial Symptom Assessment Scale—Heart Failure
ELISA	Enzyme-linked immunosorbent assay
HIPAA	Health Insurance Portability and Accountability Act
EDTA	Ethylenediaminetetraacetic acid
BHT	Butylated hydroxytoluene

1. BACKGROUND:

Heart failure

Although significant advancements in morbidity and mortality statistics have been established with medical treatment, HF remains a prevalent, morbid, and costly condition.[1,2] Currently, 6.5 million Americans have heart failure (HF),[1,3,4] 50% are readmitted within 6 months of hospital discharge for exacerbations of HF.[5,6] Thus, hospitals are financially penalized for HF readmissions within 30 days based on the Readmissions Reduction Program initiated by the Centers for Medicare & Medicaid Services. Moreover, patients with HF continue to be symptomatic even after optimization of medical treatment. These symptoms are associated with frequent hospitalization, as well as decreased health related quality of life (HRQOL).[7,8] Therefore, HF symptom reduction is still the major target of treatment to reduce frequent re-hospitalizations and improve HRQOL.[7,8]

Vitamin C Supplementation

Mean serum vitamin C level was significantly lower in patients with HF compared to those with other non-HF chronic illness.[9-11] Up to 39% of patients with HF had vitamin C deficiency.[10] Many studies have shown that higher vitamin C levels are associated with improved endothelial function.[12-14] There was a significant positive correlation between cardiac function and serum vitamin C level.[15-17] Furthermore, in a prospective study in HF, vitamin C deficiency predicted shorter cardiac event-free survival.[11]

In two intervention studies in patients with HF,[11,12] investigators found that vitamin C supplementation increased serum vitamin C level[18] and also improved endothelial function.[13,17] Other interventional studies also provided evidence that vitamin C supplementation not only improved cardiac function,[4,12,19] but also reduced oxidative stress in patients with HF.[13,20] However, most of these trials tested effects of high dose vitamin C supplementation via intra-venous or intra-arterial administration. Only two trials with very small sample size (n=10) tested oral, 1 month vitamin C supplementation and found vitamin C supplementation increased serum vitamin C level and also improved endothelial function, although neither study controlled for confounders such as age, race, sex, BMI or social status.[13,17]

Preliminary Study

The PI has conducted a preliminary study that serves as the foundation for this feasibility pilot proposal. This was an observational study in which we collected dietary vitamin C intake from a 4-day food diary, symptom burden using the Memorial Symptom Assessment Scale—Heart Failure, and HRQOL using the Minnesota Living with Heart Failure questionnaire at baseline, and prospectively followed cardiac hospitalization and death for up to 4 years in 264 patients with HF. In this study, 41% of HF patients had vitamin C deficiency. Patients with vitamin C deficiency had higher symptom burden ($p = .05$), worse HRQOL ($p < .001$) and were about twice as likely to have a cardiac event compared to patients with adequate vitamin C intake ($p = .015$). This study demonstrated the high prevalence and worse consequences of vitamin C deficiency in patients with HF.

2. STUDY OBJECTIVE

The purpose of this study is to test a low-cost, simple vitamin C supplementation intervention, that is, comparing placebo to 500mg/day vitamin C and 1gram/day vitamin C daily to assess feasibility and acceptability of vitamin C supplementation and effects on serum vitamin C level, cardiac function, HF symptoms, and HRQOL. Our specific aim 1 is to test the effect of a vitamin C supplementation intervention on the primary outcome (serum vitamin C level) from baseline to 3-month follow-up among 3 groups (0.5 g, 1 g vitamin C, and placebo).

Specific aim 2 is test the effect of a vitamin C supplementation intervention on the secondary outcomes (HF symptom burden, health related quality of life (HRQOL), cardiac function, and oxidative stress) from baseline to 3-month follow-up among 3 groups. Specific aim 3 is to collect data to assess feasibility (recruitment, retention, attrition rates).

3. INVESTIGATIONAL PLAN

Design. This project is a feasibility pilot study to test the effects of vitamin C supplementation, and to obtain initial estimates of effect size to support a future RCT. The proposed vitamin C supplementation intervention study is a three-group, single blind, placebo controlled prospective design (control n=14, Vit C 500mg n=14, Vit C 1000mg n=14). The most commonly tested dose of vitamin C in current trials on vitamin C supplementation is 1 g/day.[18] The primary endpoint to evaluate the effect of vitamin C supplementation is serum vitamin C level. The secondary outcomes include HF symptom burden, HRQOL, cardiac function, and oxidative stress. The variables would be measured in person at baseline and at 3 months include: HF symptom burden, HRQOL, PROMIS fatigue, depression and sleep disturbance, serum vitamin C level, biomarker of cardiac function (i.e., cardiac output using impedance cardiograph) and oxidative stress (8-iso-PGF2a isoprostane, see below in detail), as well as demographic, clinical, and other variables that can affect study outcomes (e.g., age, gender, race/ethnicity, body mass index, serum creatinine) and medications. HF symptom burden and HRQOL will also be measured at Month 1 and 2 by phone. We will also collect data to assess feasibility (recruitment, retention, attrition rates).

Sample and Setting. A total of 42 participants (14 per group) will be randomly assigned to either the control or the intervention group. Patients with HF will be recruited at the University of North Carolina Hospital internal medicine/cardiology outpatient clinics.

Inclusion/Exclusion Criteria. Inclusion criteria include patients (a) have a diagnosis of chronic HF. The diagnosis and etiology of chronic HF will be confirmed by a HF cardiologist using established criteria,[6,21,22] (b) have undergone evaluation of HF and optimization of medical therapy, (c) are not taking any vitamin C supplementation at all or are willing to stop taking their current vitamin C supplementation, (d) able to read and speak English, (e) have >1 month from any inpatient hospitalization, (e) treating cardiology healthcare provider indicates the individual is a good candidate for this study that involves 3 months of vitamin C supplement of 500 mg/day, 1g/day, or placebo, (f) Per treating healthcare provider's assessment, patient's projected lifespan is greater than or equal to 6 months.

Exclusion criteria include: (a) stage D HF or New York Heart Association (NYHA) functional class IV, (b) history of renal stones or renal disease (serum creatinine >1.5), (c) history of glucose-6-phosphate dehydrogenase deficiency (G6PD) and (d) cognitive impairment that precludes giving informed consent or ability to follow protocol instructions, (e) originally taking vitamin C 500mg/day or more, (f) women who are pregnant.

Female patients with HF are considered past child-bearing potential: 1) if they are ≥60yrs of age or 2) if they are age 50 to 59 years and have not menstruated for 12 months (will confirm by self-report). For women < 50 years old (with child-bearing potential), we will confirm by self-report that they are not pregnant and confirm this by completing a urine pregnancy test prior to enrollment and assess for likelihood of pregnancy on a monthly basis.

4. INTERVENTION

The intervention is designed to complement medical management. Therefore, all patients will continue to be medically managed by their health care provider as usual.

Participants will have a visit at baseline and Month 3 (with some flexibility to do the final visit at 3 months +/- 1 month) coordinated with their regular clinic visits that are typically scheduled every 3 months.

Vitamin C supplementation. Throughout the study, patients will continue with their routine diets. Patients randomized to the intervention groups will be provided with 4-month supply of either Vitamin C 500mg or Vitamin C tablets (1000mg) in a bottle and the control group will be provided placebo tablets in a bottle. All participants in the intervention group will be instructed to take one vitamin C tablet (500mg/ day or 1000mg/day) with one meal daily from baseline for 3 months and all control group participants will be instructed to take one placebo tablet with one meal daily from baseline to 3 months. Participants will return their un-used investigational drugs on the day of their 3-month follow-up. We will count remaining pills to determine participant's treatment adherence with both the vitamin C supplementation (500mg or 1000mg) and control (placebo) groups. After counting the pills, the un-used pills will be delivered to the Investigational Drug Services (IDS) pharmacy to dispose. We will draw blood to measure serum vitamin C level to determine drug accountability.

Role of the Investigational Drug Services (IDS). The IDS will provide oversight for the storage, dispensing, labeling, distribution and disposal of all investigational medications (vitamin C tablets and placebo) for the study.

5. PROCEDURES AND RECRUITMENT STRATEGY

Permission for this study will be obtained from the University of North Carolina at Chapel Hill Institutional Review Board. A dedicated and trained research assistant will recruit HF patients from the UNCH clinics. A list of HF patients who will come to the UNCH clinics will be generated and obtained from the staff in charge for the scheduling information in the clinics one week before patients' visits. On the day that the potential participants come to the clinic, the research assistant will screen the potential participant's eligibility based on inclusion and exclusion criteria. The research assistant also will consult with the potential participant's treating healthcare provider to make sure the potential participant is appropriate for the study and patient's projected lifespan is greater than or equal to 6 months. Once the research assistant confirms the potential participants are eligible and gets approval from the provider, the research assistant will approach and briefly explain the study to recruit potential participants while they wait to see their physicians. If potential participants are interested in participation, the research assistant will then confirm eligibility. For eligible patients, study requirements will be explained in detail. If the patient agrees to participate, a signed informed consent will be obtained based on consent process (see below) and we will administer the survey, measure cardiac impedance and obtain the blood samples. All eligible patients will be randomized to either the control group or to the intervention group using the Medsharing application for clinical trials.

*Baseline visit***.** Data on socio-demographics, clinical characteristics medications, symptom burden, PROMIS depression, fatigue, and sleep disturbance, HRQOL, will be collected at the beginning of the visit and blood will be drawn to measure serum vitamin C level and oxidative stress (8-iso-PGF2a isoprostane). All participants will be asked to return their respective supplementation bottles to the research assistant at Month 3. We will count pills to determine patient adherence to taking the placebo or vitamin C supplementation.

*Follow up phone call (Month 1 and 2)***.** Follow up phone calls will occur within 1 week after enrollment to follow-up whether they are taking the investigational pills (vitamin C or placebo) daily and whether they have any adverse events from taking the investigational pills, as well as at Month 1 and 2. The research assistant will inquire about general welfare and collect data on HF symptom burden and HRQOL (for both groups).

*Month 3 visit***.** Data on socio-demographics, clinical characteristics medications, symptom burden, PROMIS depression, fatigue, and sleep disturbance, HRQOL, will be collected at the beginning of the visit and blood will be drawn to measure serum vitamin C level and oxidative stress (8-iso-PGF2a isoprostane). All participants will be asked to return their vitamin C (or placebo) bottle to the research assistant at Month 3. We will count pills to determine their adherence to taking the placebo or vitamin C supplementation.

6. CONSENT PROCESS

The consent process includes: 1. Obtain written informed consent from the study subject; 2. Ensure that the most recent version of the IRB-approved consent/HIPAA authorization form is used; 3. Review the informed consent/HIPAA authorization form with the subject in a location that allows privacy; 4. Allow the subject time to read the document and ask questions. Encourage input from family members, if appropriate; 5. Ensure that the subject signs and dates the document in the required sections of the consent and HIPAA authorization form; 6. Ensure the consenter signs and dates (same date) the document in the required section of the consent form; 7. Provide a singed copy of the informed consent/HIPAA form document to the subject; and 8. Document and date consent procedure and file the signed document and checklist back to locked cabinet.

The data (from self-report, impedance cardiograph, and blood drawn) will be collected at baseline clinic appointment and Month 3 in person for all patients. HF symptom burden and HRQOL will be collected at baseline and Month 3, in person and also Month 1 and 2, by phone. All patients will be compensated up to $50 for participating in this study: $25 at baseline visit and $25 at Month 3 visit.

Under special circumstances that we are not allowed to collect in-person data at Month 3 (such as Covid-19 pandemic stay-at-home order that prevents our in-person data collection), we will not collect data from impedance cardiograph or blood drawn. We will only collect self-report data using one of the following 2 ways based on subjects' preference: 1) by phone; 2) by mail--we will send subjects the questionnaires ahead of time and ask them to complete and send the questionnaire back to us. We also will ask them to send their un-used vitamin C pills back to us by mail.

7. MEASUREMENTS AND STUDY EVALUATIONS

Serum vitamin C level. We will measure participant's serum vitamin C level at baseline and Month 3 to measure the effect of vitamin C supplementation. Sample vitamin C will be measured in serum using MyBioScouce ELISA kits.

Symptom burden. Physical symptom burden will measured using items from the Memorial Symptom Assessment Scale—Heart Failure (MSAS-HF).[8,23] The MSAS-HF is an 8-item questionnaire adapted from Portenoy's Memorial Symptom Assessment Scale that is designed to provide multidimensional information about HF symptoms experienced by patients with HF. Patients will be first asked if the symptom was present during the previous 7 days. If present, three characteristics of each symptom will be rated: frequency of symptom, severity of symptom, and degree of symptom distress. Frequency is rated on a scale from 1 to 4 (rarely to almost constantly), severity rated on a scale from 1 to 4 (mild to very severe) and distress rated on a scale from 0 to 4 (not at all to very severe). Burden score for each symptom can range from 0 (no burden) to 12 (greatest symptom frequency, severity, and distress). The scale has good reliability, ranges of 0.73-0.92 in patients with HF.[8,23]

Health-related quality of life (HRQOL). The Minnesota Living with Heart Failure questionnaire (MLHFQ) is a measure of HRQOL that assesses the patient's perceptions of the

influence of HF on physical and emotional aspects of life.[24,25] The 21 items are summed with higher scores indicating worse HRQOL. The questionnaire has been widely used to measure quality of life in this population. Researchers have demonstrated evidence for validity and reliability (Cronbach's alphas ranging from .88 to .93).[24-26] The MLHFQ was used in our study that demonstrated a significant relationship between vitamin C deficiency and HRQOL, as well as between HRQOL and re-hospitalization or mortality.[26]

Cardiac function. Impedance Cardiography is a measurement method that is primarily used to determine aspects of Cardiac Output (CO) that we will use the MindWare Mobile impedance cardiograph (model number 50-2303-00) in this study. CO is the total amount of blood, pumped from both the left and right ventricles of the heart for each of its successive systolic phases, over the course of one minute. Left ventricular cardiac output is the CO from the left ventricle only and can be estimated via a non-invasive technique called Impedance Cardiography (ICG), which provides an approximation of Stroke Volume (SV) (CO=SV*HR). We will measure patient's cardiac output and heart rate variability to reflect the participant's cardiac function using impedance cardiograph that is non-invasive, reproducible, valid and widely used in patients with cardiovascular disease.[27] The MindWare Mobile impedance cardiograph is a commercially available impedance cardiograph that has been widely used in research studies.[28] The MindWare Mobile impedance cardiograph is a small, portable device with a high precision frequency constant current of 400 micro amps which allows measurement of the impedance changes across the thorax to monitor cardiac function.[28]

Oxidative stress biomarker. We will measure 8-iso-PGF2a isoprostane as a biomarker of oxidative stress. Elevated level of 8-iso-PGF2a isoprostane will serve as a biomarker of increased lipid peroxidation due to oxygen free radical production exceeding antioxidant capacity and will be measured in our Biobehavioral Lab. The level of the biomarker is expected to decrease in response to the vitamin C supplementation. Venous blood will be drawn into vacutainers containing trisodium citrate, EDTA and/or BHT depending on the analysis, centrifuged in a refrigerated centrifuge and serum separated and allotted to micro-tubes and kept at -70^{o}C prior to analysis. 8-iso-PGF2a isoprostane will be measured in serum using Cell Biolabs ELISA kits. For all assays, samples and standards will be run in duplicate and inter- and intra-assay determined to assure accuracy and reproducibility.

Covariates. We will collect participants' demographic and clinical data to assess sample characteristics, characterize the sample, and obtain data on potential confounding variables.

8. SAFETY EVALUATIONS

All participants will receive a phone call within 1 week after enrollment, and also at Month 1 and Month 2 to follow-up whether they are taking the investigational pills (vitamin C or placebo) daily and whether they have any adverse events from taking the investigational pills (see checklist in Appendix). If any adverse events were found/reported, we will follow them per recommendations of the medical monitor until the event resolves. Sarah Waters, a nurse practitioner with specialty in heart failure management at UNC Meadowmont Cardiology clinic will serve as a medical monitor on this study. Any adverse event will be reported to Sarah Waters in 72 hours or less. Sarah Waters will determine the severity of the adverse events and advise whether the participant needs to stop taking the investigational pills, withdraw from the study, or any medical treatment is needed. We will follow Sarah Waters' advice immediately.

When subjects have AE (define as new signs and symptoms after taking investigational drugs, such as digestive distress--diarrhea, nausea, abdominal bloating and any other unanticipated adverse events that could possibly be related to the intervention). We will report to

Sarah Waters to determine the severity of the AEs (see below). When mild AE is determined, subjects will continue to take their investigational drugs without further treatment and the RA will keep following up subject's AE until AE resolves. When moderate AE is determined, we will ask subjects to stop taking their investigational drug, advise them to seek medical treatment, and continue to follow up until the AE resolves. If severity of any AE is more than moderate, we will ask subjects to seek for emergent medical treatment.

- Mild Adverse Event – Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache).
- Moderate Adverse Event – Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication).
- Severe and undesirable Adverse Event – Event results in significant symptoms that prevents normal daily activities; may require hospitalization or invasive intervention (e.g., anemia resulting in blood transfusion).

The adverse event information will be reviewed in our monthly team meeting to monitor subject safety. The PI will also monitor the rate of AEs occurring in this study and decide if it is reasonable in light of the rate of AEs in the current literature to continue the study with the medical monitor's input.

The research assistant is responsible to report any AE related to the study to Sarah Waters and the PI. The PI will work with the medical monitor to evaluate the event and make a determination of relatedness if the event is related to the study, as it occurs and for notifying the Associate Dean for Research of the UNC School of Nursing and UNC IRB of the occurrence of any adverse event. A scale on relatedness ranging from "Not related to" to "Definitely related to" (Not related to, probably not related to, possibly related to, definitely related to) will be used to evaluate relatedness. Any "definitely related" and "possibly related" events will be reported to the UNC IRB.

The PI will report to the UNC IRB any adverse events that are (1) unexpected, (2) related or possibly related to participation in the research, and (3) serious or suggest that there are new or increased risk(s) to subjects.

Patient Safety and Confidentiality. All private health information (PHI) will be kept strictly confidential and subject to the Health Insurance Portability and Accountability Act (HIPAA). All study data in transit will be stored on an encrypted lap top computer stored and locked within the office of the study PI. All transit study data will be back up to the secure SON server that is password protected and maintained by information technology support and then be deleted from the encrypted laptop computer within 72 hours after data are collected. The secure SON server can only be accessed by study personnel on this study. Any new signs or symptoms reported by the patient to the research team will be promptly communicated to the patient's health care team. At the baseline visit, patients will be assessed for any vitamin supplementation, serum creatinine and history of kidney stones. If subjects are currently taking a vit C supplement, we will advise them to stop taking any vitamin C supplement while they are on the study. We also will carefully review with the subjects if they are taking any multivitamin that contains vitamin C and advise them to stop taking any multivitamin that contains vitamin C. Although vitamin C is a water-soluble vitamin, we have implemented these steps to insure safety before randomization.

9. DATA MANAGEMENT AND STATISTICAL ANALYSIS

Each participant will be assigned an anonymous ID. Data will be collected using touchscreen laptop computer, and the REDCap (Research Electronic Data Capture) system,[29,30] a secure web-based application that is designed to support data capture for research studies.[30]

All data analyses will be performed using SPSS 24.0. All estimates will be obtained along with 95% confidence intervals.

Descriptive statistics: All data with approximately symmetric distributions will be described by their mean and standard deviation, as well as number/frequency and percentage (for Aim 3) and variables with skew will be described by the median and interquartile range. Categorical variables will be shown as total number and proportion and will include: race, sex, NYHA functional class, and comorbidity. Associations between categorical variables will be tested by the Chi Square test (X^2) or McNemar's test. Continuous variables will include symptom burden, PROMIS depression, fatigue, and sleep disturbance, HRQOL, cardiac function, serum vitamin c levels and biomarker for oxidative stress. Associations between categorical and continuous variables will be tested by t-test and analysis of variance (ANOVA). Associations between continuous variables will be tested using Pearson's correlation coefficient (r) will be used to establish if the correlation coefficient is statistically different.

Efficacy analysis for the specific aims is described below:

The primary endpoint is serum vitamin C level. For Aim 1 to test the effect of a vitamin C supplementation intervention on the primary outcome (serum vitamin C level) from baseline to 3-month follow-up among 3 groups, we will use repeated measure of ANOVA to detect differences in the serum vitamin C level from baseline to 3-month follow-up in the intervention group and compared to the control group from baseline to 3-month follow-up.

The secondary endpoints are symptom burden, HRQOL, cardiac function, and oxidative stress. For Aim 2 to test the effect of a vitamin C supplementation intervention on the secondary endpoint of HF symptom burden from baseline to 3-month follow-up among 3 groups, we will use repeated measure of ANOVA to detect differences in symptom burden from baseline to 3-month follow-up in the intervention group and compared to the control group from baseline to 3-month follow-up. Similarly, to test the effect of a vitamin C supplementation intervention on the secondary endpoint of HRQOL (cardiac function, and oxidative stress) compared to the control group, we will use repeated measure of ANOVA to detect differences in HRQOL (cardiac function, and oxidative stress) from baseline to 3-month follow-up in the intervention group and compared to the control group from baseline to 3-month follow-up.

Similar analysis will be done for adverse events. to test the effect of a vitamin C supplementation intervention on the frequencies of advance events compared to the control group, we will use ANOVA to compare frequencies of adverse events during the 3-month period among 3 groups.

Sample Size and Power: The total sample size of 42 participants will be selected as a pilot feasibility study. With 42 patients (14 in each group) and an alpha level of .05, the power of the ANOVA F test to detect a significant group difference will be 80% if the effect size is 0.5.

Interim/safety Analysis. We plan to conduct the interim/safety analysis when we have 50% of the intervention sample, and the findings (as well as adverse events) will be reported to the medical monitor. The medical monitor will make decisions about the safety of continuing (or stopping) the protocol, providing recommendations for recruitment, retention, safety, and other issues as appropriate.

10. APPENDIX:

Checklist of adverse events for taking high dose of vitamin C supplement

Study #: _____ Data collector: _____

Date of follow-up: _____(for ☐Week 1, ☐Month1, ☐Month2, ☐Month3)

1. Diarrhea ☐Yes ☐No
2. Nausea ☐Yes ☐No
3. Abdominal bloating ☐Yes ☐No
4. Others: any other unanticipated adverse events/problems that occurred ☐Yes ☐No _____(described what it is)

If any yes for item 1-4, describe in the box: 1) when did the event start, 2) how long did it last, 3) did the participant take any treatment/action, and 4) is it now resolved?

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