ORIGINAL RESEARCH

A Pilot Randomized Crossover Trial Assessing the Safety and Short-Term Effects of Pomegranate Supplementation in Hemodialysis Patients

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Objective: Oxidative stress and systemic inflammation are highly prevalent in patients undergoing maintenance hemodialysis (MHD) and are linked to excess cardiovascular risk. This study examined whether short-term supplementation with pomegranate juice and extract is safe and well tolerated by MHD patients. The secondary aim was to assess the effect of pomegranate supplementation on oxidative stress, systemic inflammation, monocyte function, and blood pressure.

Design: Prospective, randomized, crossover, pilot clinical trial (NCT01562340).

Setting: The study was conducted from March to October 2012 in outpatient dialysis facilities in the Seattle metropolitan area.

Subjects: Twenty-four patients undergoing MHD (men, 64%; mean age, 61 ± 14 years) were randomly assigned to receive pomegranate juice or extract during a 4-week intervention period. After a washout period, all patients received the alternative treatment during a second 4-week intervention period.

Intervention: Patients assigned to receive pomegranate juice received 100 mL of juice before each dialysis session. Patients assigned to receive pomegranate extract were given 1,050 mg of extract daily.

Main Outcome Measures: The main outcome measures were safety and tolerability of pomegranate juice and extract. Additional secondary outcomes assessed included serum lipids, laboratory biomarkers of inflammation (C-reactive protein and interleukin 6) and oxidative stress (plasma F2 isoprostanes and isofurans), monocyte cytokine production, and predialysis blood pressure.

Results: Both pomegranate juice and extract were safe and well tolerated by study participants. Over the study period, neither treatment had a significant effect on lipid profiles, plasma C-reactive protein, interleukin 6, F_2-isoprostane or isofuran concentrations, predialysis systolic or diastolic blood pressure nor changed the levels of monocyte cytokine production.

Conclusions: Both pomegranate juice and extract are safe and well tolerated by patients undergoing MHD but do not influence markers of inflammation or oxidative stress nor affect predialysis blood pressure.

Introduction

CARDIOVASCULAR AND INFECTIOUS diseases are the leading causes of death in patients with end-stage renal disease (ESRD).[1] The high cardiovascular morbidity and mortality in patients undergoing maintenance hemodialysis (MHD) cannot be entirely explained by traditional risk factors, and increased oxidative stress has been identified as a key contributor to the pathogenesis of cardiovascular disease in this population.[2] Uremic oxidative stress is biochemically characterized as a state of increased lipid peroxidation, accumulation of unsaturated reactive aldehydes and oxidized thiols, and concomitant depletion of reduced thiol antioxidant groups.[2] Levels of plasma oxidative stress biomarkers are associated with mortality in MHD patients, and accumulating evidence demonstrates that an increase in oxidative stress may play a central role in uremic complications.[3] Chronic systemic inflammation may in turn further exacerbate oxidative stress and along with endothelial dysfunction may act synergistically to accentuate cardiovascular disease and infection-related complications in MHD patients.[4,5]

Given the robust clinical and experimental data linking oxidative stress with excess morbidity and mortality in dialysis patients, there is a compelling rationale for investigating whether novel antioxidant therapies reduce these complications. Polyphenols derived from pomegranate juice have not been adequately studied in clinical trials and represent a potential therapy for hemodialysis patients. Polyphenols have been shown to confer antioxidant protection,

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reduce platelet aggregation, induce vasorelaxation, and reduce inflammation in humans.[6–8] Several studies suggest that dietary phenols, including those derived from pomegranate juice, may have beneficial effects in patients undergoing dialysis, including reduced infectious and cardiovascular complications, decreased levels of inflammatory biomarkers, improved lipid profiles, and lower systolic blood pressures.[9–11]

The primary objective of this study was to test the hypothesis that 4-week administration of pomegranate juice and/or extract is safe and well tolerated in MHD patients. We also assessed whether 4-week pomegranate juice and/or extract supplementation influenced biomarkers of oxidative stress or systemic inflammation or affected predialysis blood pressure.

Methods

Study Design and Participants

This was a prospective, randomized, open-label, crossover trial (NCT01562340). Study participants were recruited from Northwest Kidney Centers outpatient dialysis facilities in the Seattle metropolitan area from March through October 2012 with the following inclusion criteria: ESRD patients receiving thrice-weekly hemodialysis for at least 90 days, aged 18 to 85 years, life expectancy greater than 1 year, and the ability to provide informed consent for study participation. Exclusion criteria included AIDS; active malignancy excluding basal cell carcinoma of the skin; gastrointestinal dysfunction requiring parenteral nutrition; history of poor adherence to hemodialysis or medications; kidney transplant less than 6 months before study enrollment; anticipated live donor kidney transplant over the study duration; patients taking vitamin E supplements (60 IU/day or more), vitamin C (500 mg/day or more), or other antioxidant or nutritional supplements during the 30 days before enrollment; patients hospitalized for more than 5 days within the 30 days preceding enrollment; and patients with a history of a major atherosclerotic event (myocardial infarction, urgent target vessel revascularization, coronary bypass surgery, and stroke). The University of Washington Institutional Review Board approved the study, and all patients provided written informed consent before study enrollment.

Study Procedures

A total of 57 patients were assessed for eligibility, 35 gave consent, and 24 were randomized (Fig. 1). Patients were randomly assigned to 1 of 2 study groups in a 1:1 ratio to either 4 weeks of pomegranate juice (100 mL administered to subjects immediately before each dialysis treatment) followed by 4 weeks of pomegranate juice extract (1,050 mg

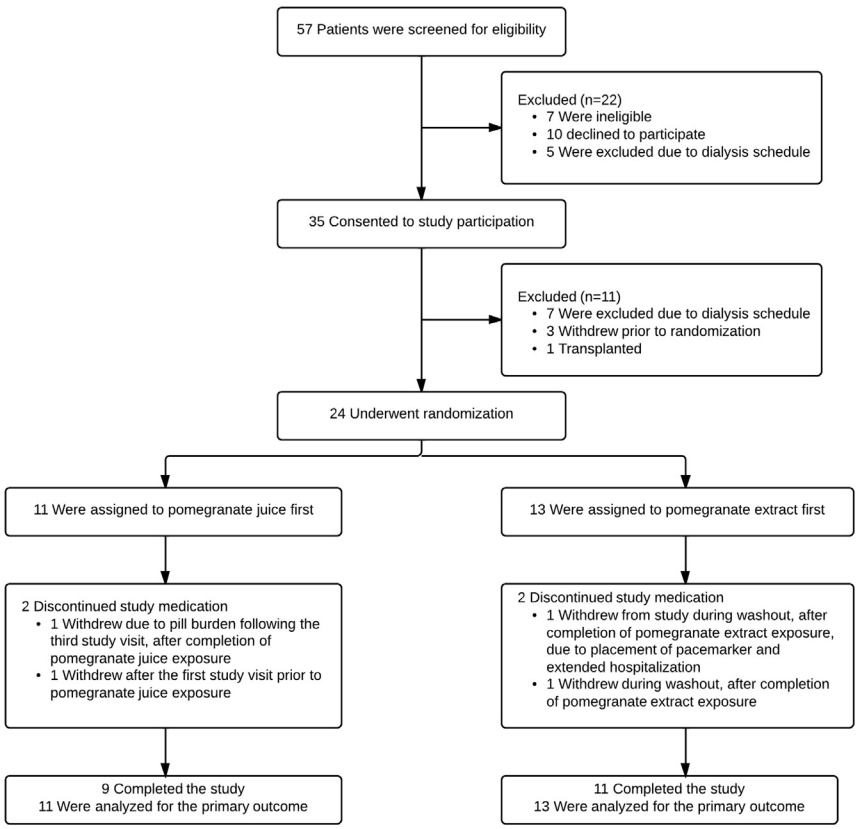

Figure 1. Flow chart of study populations, including the number of patients who were screened, gave consent, underwent randomization, completed the study treatment and were analyzed for the primary outcome.