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A prospective randomized wait list control trial of intravenous iron sucrose in older adults with unexplained anemia and serum ferritin 20–200 ng/mL

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ABSTRACT

Anemia is common in older persons and is associated with substantial morbidity and mortality. One third of anemic older adults have unexplained anemia of the elderly (UAE). We carried out a randomized, wait list control trial in outpatients with UAE and serum ferritin levels between 20 and 200 ng/mL. Intravenous iron sucrose was given as a 200-mg weekly dose for 5 weeks either immediately after enrollment (immediate intervention group) or following a 12-week wait list period (wait list control group). The primary outcome measure was changed in 6-minute walk test (6MWT) distances from baseline to 12 weeks between the two groups. Hematologic, physical, cognitive, and quality of life parameters were also assessed. The study was terminated early after 19 subjects enrolled. The distance walked in the 6MWT increased a mean 8.05 ± 55.48 m in the immediate intervention group and decreased a mean 11.45 ± 49.46 m in the wait list control group ($p = 0.443$). The hemoglobin increased a mean 0.39 ± 0.46 g/dL in the immediate intervention group and declined a mean 0.39 ± 0.85 g/dL in the wait list control group ($p = 0.026$). Thus, a subgroup of adults with UAE may respond to intravenous iron. Enrollment of subjects into this type of study remains challenging.

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Introduction

Anemia is common in older adults, with a prevalence of approximately 10% in community-dwelling men and women aged 65 and older, rising to 20–35% in those aged 85 and above [1,2]. Although on an individual basis anemia in older adults is frequently overlooked or ignored, studies from numerous older populations throughout the developed world have consistently demonstrated an association between anemia, which is typically mild, and poor clinical outcomes, including decreased physical performance and strength [3,4], decreased mobility function [5], impairment in instrumental activities of daily living [6],

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Table 1
Study entry criteria.

Inclusion criteria	Exclusion criteria
1. Age ≥ 65 years old 2. Hemoglobin concentration ≥ 9.0 g/dL and <11.5 g/dL for women and ≥9.0 to <12.7 g/dL for men 3. Unexplained anemia (see Table 2 for identifiable etiologies of anemia that investigator must review) 4. Serum ferritin level ≥ 20 and ≤200 ng/mL 5. Able to walk without the use of a walker or motorized device, or the assistance of another person 6. Able to understand and be willing to provide written informed consent in the absence of dementia, defined as a Montreal Cognitive Assessment score ≥ 22 7. Able to understand and speak in English, or at select sites where Spanish-speaking study staff and written informed consent in Spanish are available and approved by the institutional review board, Spanish-speaking subjects who do not speak English may be enrolled	1. Red blood cell transfusions in the past 3 months 2. Use of erythropoiesis stimulating agent in the past 3 months 3. Intravenous iron infusions in the past 3 months 4. Distance on baseline 6-minute walk test above age- and sex-adjusted population median 5. History of unstable angina or myocardial infarction in the past 3 months 6. History of stroke or transient ischemic attacks in the past 3 months 7. Uncontrolled hypertension defined as greater than the average diastolic blood pressure > 100 mm Hg or systolic blood pressure > 160 mm Hg on 2 separate occasions on 2 separate days during screening 8. Positive fecal occult blood test within the screening period 9. Elevated aspartate aminotransferase or alanine aminotransferase ≥ 2 × upper limit of normal 10. Documented anaphylactic reaction to iron sucrose infusion in the past 11. Initiated on oral iron supplementation within the last 6 weeks, or within the last 3 months and having at least a 1 g/dL improvement in hemoglobin since starting oral iron supplementation

increased frailty [7], impaired quality of life [8], decreased cognitive function [9], and increased mortality [10,11].

Anemia has many causes. Data from large population-based surveys have ascertained several broad etiologies of anemia in older adults: iron deficiency that is possibly nutritional but more often secondary to blood loss, anemia associated with inflammation, anemia due to renal insufficiency, anemia due to nutritional deficiencies, and unexplained anemia of the elderly (UAE). UAE, a relatively new diagnostic category, is consistently found in approximately 30–44% of older anemic subjects [1,2,12]. Prospective studies incorporating a thorough clinical evaluation have demonstrated similar proportions of UAE [13,14]. Iron deficiency in older adults may be difficult to identify, with the diagnosis confirmed only by response to a trial of iron supplementation [13]. In addition, patients who do not respond to oral iron may have a rise in hemoglobin following the administration of intravenous iron [15]. The Partnership for Anemia: Clinical and Translational Trials in the Elderly (PACTTE) consortium was formed to investigate treatment strategies in subjects with UAE. This study was designed as the first PACTTE interventional study, utilizing intravenous iron sucrose (IVIS) in a subset of subjects with UAE.

Materials and methods

Study design

The study was designed as a randomized, wait list control trial. Subjects were randomized to receive IVIS either immediately after enrollment (immediate intervention group) or after an initial waiting period of 12 weeks (wait list control group). The protocol was approved by an independent data and safety monitoring board (DSMB) as well as the institutional review board at each participating institution, and the trial was conducted in accordance with the Declaration of Helsinki for biomedical research involving human subjects. Written informed consent was provided by all subjects. The trial was designed, implemented, and overseen by the PACTTE Steering Committee. An independent DSMB reviewed the safety data and study progress on an ongoing basis.

Participants

Outpatient men and women with the following criteria were eligible to enroll: age ≥65 years with a hemoglobin concentration of ≥9 g/dL and <11.5 g/dL for women or <12.7 g/dL for men with unexplained anemia; serum ferritin between 20 and 200 ng/mL (inclusive); ability to walk without the use of a walker or motorized device, or the assistance of another person; lack of significant cognitive impairment defined by a Montreal Cognitive Assessment score of 22 or higher; and ability to understand and speak English (Table 1). The protocol initially included subjects with a serum ferritin between 20 and 100 ng/mL (inclusive) but was modified on March 26, 2012, due to poor recruitment to allow serum ferritin levels between 20 and 200 ng/mL (inclusive). The protocol was additionally modified on August 20, 2012, at sites with Spanish-speaking study staff to include subjects who were able to speak and understand Spanish. Unexplained anemia was defined, similar to published criteria [13,14], as not meeting criteria for any known etiology of anemia, including vitamin B12, folate, or iron deficiency (defined as serum ferritin < 20 ng/mL); renal insufficiency (defined as glomerular filtration rate of less than 30 [16] using the four-variable Modification of Diet in Renal Disease equation [17]); thyroid dysfunction; myelodysplastic syndrome; anemia of inflammation; plasma cell dyscrasia; thalassemia trait; alcohol overuse; any prior history of hematologic malignancy; unexplained splenomegaly or lymphadenopathy; or the presence of any condition reasonably assumed to be causing anemia and not corrected for 3 months (Table 2). Subjects were excluded if they had received a red blood cell transfusion, intravenous iron, or an erythropoiesis stimulating agent within 3 months prior to enrollment; had unstable angina, a myocardial infarction, a stroke, or a transient ischemic attack within 3 months prior to enrollment; had uncontrolled hypertension; had a positive fecal occult blood test during the screening period; had significant impairment in liver function; had a documented history of anaphylactic reaction to iron sucrose infusion; had recently initiated oral iron supplementation; or if the distance walked on the 6-minute walk test (6MWT) was above the median for age and sex, to avoid a ceiling effect (Table 1; Appendix A).

Randomization

Subjects were randomized to start IVIS either immediately (immediate intervention group) or after a 12-week wait list period (wait list control group) at a 1:1 ratio via an interactive voice and web response system. The randomization sequence was computer-generated with random block sizes. Neither subjects nor investigators were blinded.

Study therapy

The total administered dose of IVIS (Venofer®) supplied by Luitpold Pharmaceuticals was 1000 mg given at a dose of 200 mg per week. The