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Original Investigation

Effect of Far Infrared Therapy on Arteriovenous Fistula Maturation: An Open-Label Randomized Controlled Trial

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Background: Malfunction of the arteriovenous fistula (AVF) is an important cause of morbidity and hospitalization in hemodialysis (HD) patients. The aim of this study is to evaluate the effect of far infrared therapy on the maturation and patency of newly created AVFs in patients with chronic kidney disease stage 4 or 5.

Study Design: Randomized controlled study.

Setting & Participants: Patients with estimated glomerular filtration rate of 5-20 mL/min/1.73 m^2.

Intervention: 40 minutes of far infrared therapy 3 times weekly for a year.

Outcomes: The primary outcome is the rate of AVF malfunction within 12 months, with malfunction defined as either: (1) thrombosis without thrill for AVFs not undergoing HD or (2) receiving any type of interventional procedure due to a lower Kt/V ($<$1.2) for patients undergoing HD. Secondary outcomes include: (1) cumulative primary unassisted AVF patency, defined as time from creation of the AVF to the first episode of AVF malfunction; (2) physiologic maturation of the AVF by the definition of AVF access blood flow (Qa) $\geq$500 mL/min and AVF diameter $\geq$4 mm at 3 months; and (3) clinical maturation of the AVF suitable for HD at 1 year.

Measurements: AVF Qa was measured by Doppler ultrasonography at 2 days and 1, 2, 3, and 12 months.

Results: We enrolled 122 patients who were randomly allocated to the intervention (n = 60) and control (n = 62) groups. In comparison to controls, patients in the intervention group had higher Qa values at 1, 2, 3, and 12 months; a higher rate of physiologic maturation (90% vs 76%; $P = 0.04$) at 3 months; and a lower rate of AVF malfunction (12% vs 29%; $P = 0.02$) but higher rates of AVF cumulative unassisted patency (87% vs 70%; $P = 0.01$) and clinical maturation (82% vs 60%; $P = 0.008$) within 12 months.

Limitations: This is a single-center nonblinded study.

Conclusions: Far infrared therapy improves the access flow, maturation, and patency of newly created AVFs in patients with chronic kidney disease stages 4 and 5.

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INDEX WORDS: Arteriovenous fistula (AVF); chronic kidney disease (CKD); far infrared therapy; hemodialysis (HD); maturation.

An adequately functioning vascular access is essential for achieving uneventful hemodialysis (HD) and improving quality of life in patients treated with long-term HD. Based on recommendations in the NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines, arteriovenous fistulas (AVFs) should be the first choice among different types of vascular access on account of their lower complications and higher long-term patency.[1] However, vascular access complications still contribute to about 17%-25% of HD patient hospitalizations in the United States, at a cost of US $1 billion annually. These complications usually result from AVF malfunction caused by mechanical, medical, and genetic factors that have been reported to have significant roles in determining the patency of AVFs.[2-6]

In a previous study, we provided evidence that far infrared therapy, a convenient and noninvasive technology, can improve access flow and patency with reduction of AVF malfunction in HD patients.[7] Far infrared radiation, an invisible electromagnetic wave with a wide range of wavelengths from 5.6-1,000 μm, is used for thermal therapy.[8] As described in recent studies, far infrared therapy might enhance endothelial function and skin blood flow and decrease the frequency of some cardiovascular diseases.[9-12] Moreover, we also demonstrated that far infrared therapy may stimulate the expression of heme oxygenase 1 (HO-1).[13] In patients with advanced stages of chronic kidney disease (CKD), an important cause of malfunction of newly created AVFs is failure to mature. However, pharmacotherapy such as clopidogrel is not

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effective in making the AVF suitable for HD because it focuses on only single or limited risk factors for AVF malfunction.[14] By contrast, thermal therapy may stimulate the expression of several enzymes targeting different pathogenetic mechanisms of AVF malfunction. Because to our knowledge, the effect of far infrared therapy on AVF maturation has never been studied before, we hypothesized that it may improve AVF maturation. Thus, this study aimed to investigate prospectively the effect of far infrared therapy on the function, maturation, and patency of newly created AVFs in patients with advanced CKD.

METHODS

Patient Selection and Study Design

This study was a prospective randomized controlled trial that conformed to the Declaration of Helsinki and was approved by the Institutional Research Board of Taipei Veterans General Hospital. Recruitment began in November 2008 and ended in August 2010; follow-up of patients continued until August 31, 2011. In this study, we included patients who met the following criteria: (1) aged 18-80 years, (2) had CKD with estimated glomerular filtration rate (eGFR) of 5-20 mL/min/1.73 m^2, (3) were not anticipated to receive dialysis or kidney transplantation within the next 3 months, and (4) were undergoing AVF creation with venous end-to-arterial side anastomosis in the upper extremity. Patients with any one of the following conditions were excluded: (1) those receiving an arteriovenous graft or cuffed tunneled double-lumen catheter as the type of permanent vascular access, (2) heart failure of New York Heart Association functional class III or IV, and (3) episode of cardio- or cerebrovascular event or receiving intervention therapy within 3 months prior to screening. Patients' general data and kidney disease were recorded directly from the patients or their hospital files.

After informed consent was obtained, study participants were randomly and equally allocated to receive far infrared therapy for 12 months as the treatment group or not to receive infrared therapy as the control group in 4 randomization cycles, using computer-generated numbers. The randomized treatment assignments were sealed in opaque envelopes and opened individually for each patient who agreed to be in the study. The study was conducted with therapy and measurements of AVF access flow and laboratory tests in accordance with the trial protocol, as follows.

Far Infrared Therapy

In this study, a WS TY101N far infrared therapy unit (WS Far Infrared Medical Technology Co, Ltd) was used for therapy. The electrified ceramic plates of this emitter generate electromagnetic waves with wavelengths in the range of 3-25 μm (peak, 8 μm). The irradiating power density is 10 and 20 mW/cm^2 when the top radiator is set at a distance of 30 and 20 cm above the skin surface, respectively. In the treatment group, the top radiator was set at a height of 25 cm above the surface of the AVF, with 40 minutes of infrared therapy scheduled 3 times weekly, beginning after the second postoperative day and continuing for 12 months. Before starting HD, patients received infrared therapy at either our nephrology clinic or at home. After starting HD, patients received 40 minutes of infrared therapy 3 times weekly during HD.

Doppler Ultrasonography of AVFs

Measurement of access blood flow (Qa) was carried out by color Doppler ultrasonography (Model SSA 340A; Toshiba) 5 times, including at 2 days and 1, 2, 3, and 12 months after creation of the AVF. The procedure was performed with the patient in a supine position. A 7.5-MHz linear array transducer was placed on the skin surface above the AVF. Velocity and Qa were determined by spectral analysis of flow at the site ~3 cm upstream from the AVF anastomotic site. For patients in the intervention group, all examinations were performed and interpreted on days without infrared therapy under the supervision of the same ultrasound expert, who was masked to the intervention assignments.

Laboratory Measurements

Biochemical parameters were determined by an autoanalyzer (Model 7600-310; Hitachi). eGFR was calculated according to an equation described by Ma et al[15] for Chinese patients with CKD: $eGFR = 175 \times \text{plasma creatinine}^{-1.234} \times \text{age}^{-0.179} \times 0.79$ [if female].

Study Outcomes

The primary outcome of this study is the rate of AVF malfunction within 12 months and was defined as either: (1) thrombosis without thrill for AVFs in patients not undergoing HD or (2) receiving any type of interventional procedure (surgery or angioplasty) for the AVF due to a lower Kt/V (<1.2) for patients undergoing HD. There are 3 secondary outcomes of this study, including: (1) cumulative primary unassisted AVF patency with the definition as time from AVF creation to the first episode of AVF malfunction (ie, thrombosis or interventional procedure) with the censoring criteria of death with functioning AVF, undergoing kidney transplantation, or shifting to peritoneal dialysis therapy; (2) the rate of AVF physiologic maturation by the definition of AVF Qa $\geq$500 mL/min and AVF diameter $\geq$4 mm at 3 months after creation of the AVF, without the assistance of an interventional procedure (surgery or angioplasty); and (3) clinical AVF maturation suitable for HD (within 1 year) with the definition as the ability to place 2 needles on the AVF for HD with an extracorporeal blood flow rate at the HD machine $\geq$200 mL/min during 8 of 12 HD sessions during a 30-day suitability ascertainment period. Decisions regarding the initiation of use or the interventional procedure of the AVF were made by the participant's physicians. To detect the malfunction rate of newly created AVFs at month 12 as 36% and 15% for the control and intervention groups, respectively, we conducted a test with significance level of 0.05 and power of 0.80, assuming group sizes were equal. These rates were based on the assumption that the malfunction rate of the newly created AVF was 20% higher than that of the prevalent AVF, which were 30% and 12.5% for the control and intervention groups, respectively, according to results of our previous study.[13] Thus, the number of patients completing the study should be more than 50 for each group. With a dropout rate of 15%, the sample size required to achieve these objectives was at least 60 in each group.

Statistical Analysis

The primary analysis was intention to treat. Data were entered into Microsoft Excel and analyzed by SPSS, version 18.0, statistical software (SPSS Inc). All data were presented as mean $\pm$ standard deviation and frequency (percentage) for continuous and categorical data, respectively. The 2-sample t test or χ^2 test was used to compare differences between the intervention and control groups. The repeated measurements of Qa and AVF venous diameter were analyzed by generalized estimating equations (GEEs).[16] The GEE approach can account for possible correlations in repeated measures; therefore, it can be used to explore differences in outcomes over time and examine the effect of independent variables on overall trends. The curves of duration after AVF creation