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Safety and Efficacy of Extracorporeal Shock Wave Myocardial Revascularization Therapy for Refractory Angina Pectoris

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Abstract

Objective: To assess the safety and efficacy of extracorporeal shockwave myocardial revascularization (ESMR) therapy in treating patients with refractory angina pectoris.

Patients and Methods: A single-arm multicenter prospective trial to assess safety and efficacy of the ESMR therapy in patients with refractory angina (class III/IV angina) was performed. Screening exercise treadmill tests and pharmacological single-photon emission computed tomography (SPECT) were performed for all patients to assess exercise capacity and ischemic burden. Patients were treated with 9 sessions of ESMR to ischemic areas over 9 weeks. Efficacy end points were exercise capacity by using treadmill test as well as ischemic burden on pharmacological SPECT at 4 months after the last ESMR treatment. Safety measures included electrocardiography, echocardiography, troponin, creatine kinase, and brain natriuretic peptide testing, and pain questionnaires.

Results: Fifteen patients with medically refractory angina and no revascularization options were enrolled. There was a statistically significant mean increase of 122.3±156.9 seconds (38% increase compared with baseline; P=.01) in exercise treadmill time from baseline (319.8±157.2 seconds) to last follow-up after the ESMR treatment (422.1±183.3 seconds). There was no improvement in the summed stress perfusion scores after pharmacologically induced stress SPECT at 4 months after the last ESMR treatment in comparison to that at screening; however, SPECT summed stress score revealed that untreated areas had greater progression in ischemic burden vs treated areas (3.69±6.2 vs 0.31±4.5; P=.03). There was no significant change in the mean summed echo score from baseline to posttreatment (0.4±5.1; P=.70). The ESMR therapy was performed safely without any adverse events in electrocardiography, echocardiography, troponins, creatine kinase, or brain natriuretic peptide. Pain during the ESMR treatment was minimal (a score of 0.5±1.2 to 1.1±1.2 out of 10).

Conclusion: In this multicenter feasibility study, ESMR seems to be a safe and efficacious treatment for patients with refractory angina pectoris. However, larger sham-controlled trials will be required to confirm these findings.

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Major advances in medical therapy as well as improved revascularization techniques with coronary artery bypass surgery or percutaneous intervention have markedly improved life expectancy and quality of life in patients with coronary artery disease (CAD) over the past 3 decades.[1] Despite these therapies, 9 million people are estimated to have angina in the United States. Of these, approximately 7% of the patients (≈60,000 new patients per year in the United States) have considerable CAD burden with ischemia and intractable angina, which is not amenable to further traditional revascularization options.[2,3] *Refractory angina*, defined as persistent (>3 months) chest pain due to CAD in patients on optimal medical therapy and for whom revascularization is not feasible,[4] is a major challenge to cardiologists because treatment options are limited. New treatment options including ranolazine,[5] ivabradine,[6] enhanced external counterpulsation,[7] and spinal cord stimulation[8] have been reported to improve symptoms in patients with refractory angina. Despite these new

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therapies, patients may continue to be limited with angina or dyspnea at low work thresholds, compromising quality of life. Strategies to enhance myocardial neovascularization are under extensive investigation. Transmyocardial laser revascularization[9] has been studied extensively over the past decade but has never been fully translated to clinical use owing to its invasive nature and owing to large studies indicating no improvement in clinical symptoms. Intracoronary or myocardial stem cell,[10-12] gene,[13] and protein therapy,[14] which have exhibited promising results but are invasive in nature, are under intensive investigation.

A new therapy, extracorporeal shockwave myocardial revascularization (ESMR), has been developed in which the noninvasive application of low-intensity shock waves is used to stimulate angiogenesis through the induction of growth factors, such as vascular endothelial growth factor[15] and nitric oxide synthase,[16] as well as the recruitment of endothelial progenitor cells.[17] Preliminary studies on animal models have found safety and efficacy of ESMR in pigs with ischemia and post−myocardial infarction.[15,18] We thus performed a pilot study to evaluate the safety and efficacy of the ESMR treatment in patients with refractory angina.

PATIENTS AND METHODS

Study Design, Study Population, and Data Collection

We designed a prospective, single-arm, multicenter pilot study to assess the safety and efficacy of the ESMR therapy in patients with at least class III angina. Investigational device exemption for Cardiospec (Medispec Ltd) was granted by the Food and Drug Administration for this study, and an approval was obtained from the institutional review board at all sites. Fifteen patients were recruited as per protocol at 3 centers in the United States: University of California, San Diego (n=7); Albert Einstein Medical Center, Philadelphia (n=5); and Mayo Clinic, Rochester (n=3).

The study protocol consisted of 5 major phases. Phase I involved screening, evaluating demographic characteristics and medical history, physical examination, pharmacological single-photon emission computed tomography (SPECT), and exercise treadmill test (ETT). Inclusion and exclusion criteria are summarized in Table 1. Patients had 2 consecutive ETTs less than 2 weeks apart (but >1 day apart), with the average taken as the baseline ETT time.

During phase II, participants underwent baseline evaluation blood testing for brain natriuretic peptide (BNP), creatine kinase (CK), and troponin I as well as resting wall motion analysis with 16-segment model echocardiography to locate adequate acoustic windows for the ESMR therapy.

Phase II involved ESMR treatment with Cardiospec (for details, see the Supplemental Online Material) according to the standard protocol. The patient was positioned, connected with the electrocardiogram (ECG) monitor, and a shock wave applicator (SWA) membrane and an ultrasound probe were used to identify the target area. The SWA was connected with the ultrasound transducer and placed with the membrane in contact with the skin, and the "treatment zone" was positioned in the

TABLE 1. Inclusion and Exclusion Criteria

I. Inclusion criteria
   1. Age ≥18 y
   2. Refractory angina
      a. With ≥3 mo grade III or IV angina
      b. Despite optimal medical therapy (at least 2 of β-blockers, calcium channel antagonists, and nitrates for a minimum of 6 wk)
      c. Deemed not amenable to further revascularization by an interventional cardiologist and a cardiac surgeon
      d. With documented reversible ischemia on pharmacological (adenosine, adenosine-analog, or dipyridamole) stress single-photon emission computed tomography
      e. With exercise tolerance time of <10 min on the modified Bruce protocol

II. Exclusion criteria
   1. Life expectancy of <12 mo
   2. Refused revascularization
   3. Active endocarditis, myocarditis, or pericarditis
   4. Moderately severe or severe valvular heart disease
   5. Intraventricular thrombus
   6. Severe chronic lung disease
   7. Active or nonactive implantable devices (pacemakers, defibrillators, and abandoned leads)
   8. Malignant disease in the treatment area
   9. Participating in other drug/device studies or previous transmyocardial revascularization
   10. Unable to cooperate or terminated the screening exercise test for symptoms other than angina pectoris or equivalent
   11. Inadequate echocardiographic acoustic window for the extracorporeal shockwave myocardial revascularization therapy