How-to-do-it

Bone marrow laser revascularisation for treating refractory angina due to diffuse coronary heart disease

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Abstract

To increase the angiogenic response and clinical efficacy of TMR, the potential synergy and safety of combining TMR with concentrated autologous bone marrow derived stem cells was evaluated. Fourteen patients with diffuse coronary artery disease and medically refractory class III/IV angina who were not candidates for conventional therapies were treated using TMR in combination with intramyocardial injection of concentrated stem cells. At the time of surgery, autologous bone marrow (120 cc) was aspirated from the iliac crest and processed over 15 min into 20 cc of concentrated mononuclear cells using a centrifugal system (HARVEST, Boston, MA). A single device performed holmium: YAG:TMR (CardioGenesis, Irvine, CA) with injection of 1 cc of concentrated stem cells through three multi-holed needles into the border zone around each laser channel. There were no perioperative adverse events including no arrhythmias. Mean number of injected cells per milliliter were: total mononuclear cells (81.3 ± 10^6), CD34+ cells (0.6 ± 10^6), and CD133+ cells (0.37 ± 10^6). At 7 months mean follow-up average angina class was significantly improved (3.5 ± 0.5 vs 1.4 ± 0.5; p = 0.004). There was no death during the follow-up. Efficient delivery of stem cells combined with TMR in a single device seems to be safe and effective for treating unmanageable angina.

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1. Introduction

Current options for treating coronary artery disease include lifestyle changes in conjunction with drug therapy, percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery. However, between 1% and 3% of patients present with diffuse coronary artery disease and are not candidates for conventional revascularisation [1]. Although sole therapy TMR has demonstrated superiority over medical therapy in randomised trials, its effectiveness at angina relief is not 100%.

To increase the angiogenic response and associated clinical efficacy of TMR, the potential synergy and safety of combining TMR with a cell-based therapy was investigated. We describe our preliminary results with bone marrow laser revascularisation (BMLR) in which a single device is used to perform holmium:YAG TMR and intramyocardially inject concentrated autologous bone marrow derived stem cells.

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each patient and immediately made available for direct intramyocardial injection.

After the bone marrow aspiration the patient was repositioned supine and a limited anterior lateral left thoracotomy incision was performed through the fifth interspace. Bone marrow laser revascularisation was performed using the Phoenix hand piece (Cardiogenesis Corporation, Irvine, CA) which consists of a 1 mm flexible optical fiber connected to a 20 W pulsed holmium:yttrium—aluminium—garnet laser. Three retractable needles with multiple side holes were incorporated into the hand piece allowing injection of concentrated mononuclear cells into the border zone around each laser channel. An average of 20 laser channels (range 15—25) was created in each patient. Following creation of each laser channel the three retractable needles were deployed and 1 cc of concentrated mononuclear cells was injected intramyocardially (Fig. 1). Study endpoints to assess the safety of BMLR included any procedural adverse events including mortality.

3. Results

Fourteen patients (11 men, 3 women) with a mean age of 65.1 ± 6.1 years (range 57—78) underwent BMLR. Baseline clinical characteristics are described in Table 1. Baseline Canadian cardiovascular class was class IV in seven patients and class III in seven patients. Mean baseline ejection fraction was 54% (range 30—65). All 14 patients enrolled in the trial underwent successful BMLR without complications including no surgical mortality and no perioperative arrhythmias. With an average follow-up of 7 months (2—12 months) there were no late deaths. Average angina class was significantly improved from baseline to follow up (3.2 ± 0.5 vs 1.4 ± 0.5; p = 0.004). All patients experienced at least a two-class reduction in angina with 50% (7/14) angina free.

Mean number of injected cells per millilitre was: total mononuclear cells (81.3 × 10⁶), CD34⁺ cells (0.6 × 10⁶), and CD133⁺ cells (0.37 × 10⁶).

4. Discussion

In a recent meta-analysis the superiority of TMR versus maximal medical management at 1- and 3—5-year follow-up with regard to two-class angina improvement has been confirmed [2].

Although TMR’s superiority over medical therapy has been demonstrated in randomised trials, its effectiveness is not 100%. As a potential alternative to TMR, exogenously administered biologic substances such as growth factors and stem cells have been evaluated for the treatment of medically refractory angina. Direct intramyocardial injection of specific growth factors, such as vascular endothelial growth factor and basis fibroblastic growth factor has yielded angina improvement in inoperable patients and may positively effect left ventricular function [3]. The use of intramyocardial injection of autologous bone marrow derived mononuclear cells such as CD34⁺ and AC133⁺ stem cells has also yielded positive efficacy signals with regard to angina improvement and myocardial perfusion [4]. We have proved that the BMLR technique is safe and easily reproducible. We had no complications including arrhythmias.

Utilising TMR as a biomechanical trigger to enhance the angiogenic cascade when combined with an adjunctive biological therapy is supported by enhanced perfusion and improved mechanical function when evaluated in ischaemic animal models [5]. Patel and colleagues [6] demonstrated enhanced stem cell retention when stem cells are injected into the border zone of a laser channel suggesting the microenvironment created by the laser—tissue interaction may be important for stem cell retention in ischaemic tissue. Finally, the small, early clinical experience with TMR combined with stem cell therapy has demonstrated its safety and feasibility and the potential for improving outcomes [7,8]. Our preliminary results demonstrate the safety and feasibility of combining TMR and autologously concentrated stem cells and delivering them through a single device.

References


