Chapter 7

Long Term Effects of Intramyocardial Bone Marrow Cell Injection on Anginal Symptoms and Quality of Life in Patients with Chronic Myocardial Ischemia

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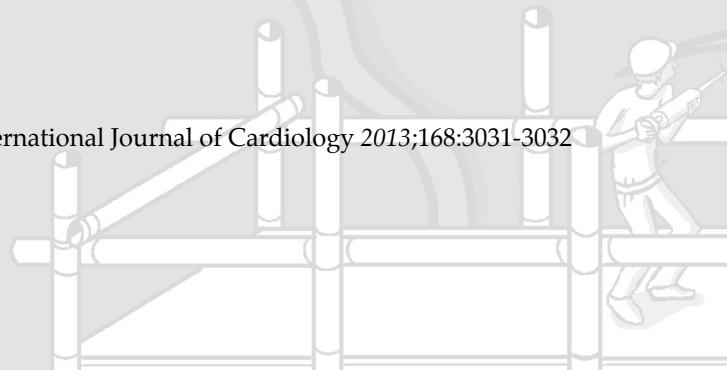

ABSTRACT

Introduction: Intramyocardial bone marrow cell injection has been proposed as a novel therapeutic option for patients with chronic myocardial ischemia. Only limited data are available on the long term effects of this treatment. The present study evaluated the long term effects of intramyocardial bone marrow cell injection in patients with chronic myocardial ischemia.

Methods and Results: In 25 patients (mean age 64±10 years, 21 men) with refractory angina and myocardial ischemia on single-photon emission computed tomography, intramyocardial injection of bone marrow-derived mononuclear cells was performed. Clinical events were monitored and anginal symptoms and quality of life were assessed at baseline, 3, 6, and 12 months follow-up and after 4 years follow-up.
After 4 years follow-up, 1 patient had died from heart failure and 2 patients died from a non-cardiac cause. No malignant arrhythmias were observed. CCS class and quality of life showed small but significant improvements compared to baseline at long term follow-up (P=0.045 and P=0.030, respectively). On an individual level, 1 out of 3 patients still experienced a reduction in anginal symptoms 4-years after bone marrow cell injection.

Conclusion: The findings of the present study demonstrate that intramyocardial bone marrow cell injection in patients with chronic myocardial ischemia is safe during longer periods of follow-up. Furthermore, the study documents that the beneficial effect of bone marrow cell injection is sustained in a minority of patients at 4-year follow-up.

Intramyocardial bone marrow cell injection has been proposed as a new therapeutic option for patients with chronic myocardial ischemia resulting from end-stage coronary artery disease not amenable to conventional revascularization. Recently, 2 randomized, placebo-controlled trials documented a reduction in anginal complaints after bone marrow cell injection in patients with chronic myocardial ischemia[1, 2]. However, only limited data are available on the long term effect of this treatment, with the longest follow-up time being 12 months[2, 3]. Therefore, we investigated the long-term safety and clinical benefit of intramyocardial bone marrow cell injection in patients with chronic myocardial ischemia.

The detailed study protocol and short-term follow-up data have been described previously[3]. In brief, 25 patients with refractory angina pectoris and stress-induced ischemia on single-photon emission computed tomography (SPECT) were enrolled into the study. After bone marrow aspiration and mononuclear cell isolation, intramyocardial cell injection was performed during cardiac catheterization using the NOGA system (BDS, Cordis, California, USA)[3]. Cell injections were targeted at myocardial segments with stress-inducible ischemia on SPECT. The study protocol was approved by the local ethics committee of our institution, and all patients provided written informed consent.

Quality of life as measured by the Seattle Angina Questionnaire[4] and clinical status according to the Canadian Cardiovascular Society (CCS) classification were assessed by an independent physician at baseline and at 3-, 6-, and 12 months follow-up. After 12 months, patients were followed up at the outpatient clinic of our hospital or were referred back to their own physician. At 4 years follow-up, patients were asked to complete the Seattle Angina Questionnaire and to visit the outpatient clinic where CCS class was assessed by an independent clinician. Data of clinical events were obtained by interviews and review of hospital records. Continuous data were compared using a mixed-model analysis of variance, with the Bonferroni correction to adjust for multiple comparisons. Changes in CCS class were analyzed by a nonparametric repeated-measures ANOVA (Friedman test), using the Wilcoxon signed-rank test for post-hoc comparisons. All tests were 2-sided, and a P value <0.05 was considered statistically significant.

At 4 years follow-up, mortality was 12% (3/25 patients). As previously reported, 1 patient died due to an intracranial hemorrhage at 7 months follow-up[3]. The second death was related to lithium intoxication at 3.5 years follow-up, and the third death was due to progressive heart failure at 3.7 years follow-up for which this patient was hospitalized 3 times previously. In addition, 2 patients were admitted (2 respectively 6

times) because of an acute coronary syndrome. In one of these 2 patients a percutaneous coronary revascularization procedure was performed at 3.5 years of follow-up. No other revascularization procedures were done. In addition, no ventricular arrhythmias were documented. One patient received a biventricular implantable cardioverter-defibrillator because of heart failure symptoms and reduced LV function.

All of the 22 patients available at 4 year follow-up completed the questionnaire and clinical evaluation. As shown in figure 1, CCS class was 3.4±0.5 at baseline, and improved significantly after 3-, 6- and 12 months to 2.4±0.6, 2.5±0.7, and 2.7±0.8, respectively. At 4 year follow-up, CCS class had declined to 3.0±0.8, comprising a modest but significant improvement as compared to baseline (P<0.001 for all time points, baseline vs. 4 year P=0.045). In accordance with this improvement, quality of life improved from 55±9% at baseline to 73±10% after 3 months, 73±15% after 6 months, and 68±13% after 12 months. At 4 year follow-up, quality of life had decreased to 61±10% (P<0.001 for all time points), but was nonetheless significantly increased as compared to baseline (P=0.030). At an individual level, 7 of 22 patients had an improved CCS class at 4 year follow-up as compared to baseline, which was paralleled by an increase in quality of life of 15±8% at 4 year follow-up. Consequently, 15 patients had similar (n=13) or worsened (n=2) CCS class, corresponding with a 2±7% increase in quality of life.

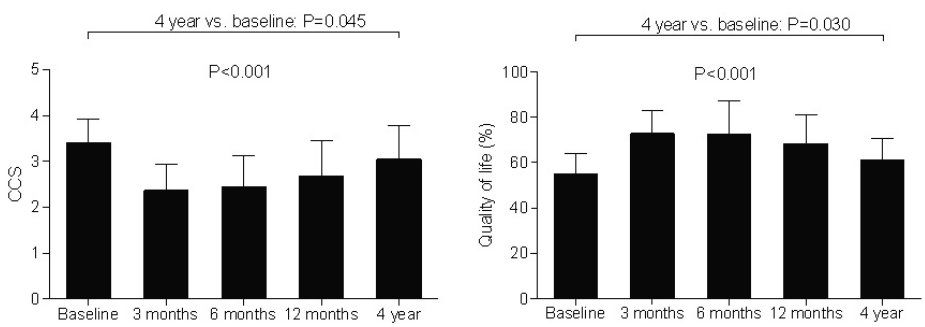

Figure 1. Anginal symptoms according to CCS class and quality of life as assessed by the Seattle Angina Questionnaire during 4-year follow-up.

Although the favorable safety profile of bone marrow-derived mononuclear cell administration has been established in patients with acute myocardial infarction, the current study is the first to describe the long term follow-up of intramyocardial bone marrow cell injection in patients with chronic myocardial ischemia. Importantly, no

malignant arrhythmias were observed. Although a number of clinical events occurred, the incidence of major cardiovascular events was not increased as compared with medically treated control groups of 2 other trials conducted in patients with chronic myocardial ischemia[2, 5]. Therefore, the results of this study suggest that intramyocardial bone marrow cell injection in patients with chronic myocardial ischemia is safe during long term follow-up.

Furthermore, the present study documents that 1 out of 3 patients still experienced a reduction in anginal symptoms 4-years after bone marrow cell injection. On the other hand, in 2 out of 3 patients anginal complaints had increased to baseline levels or worse. Probably, the duration of treatment effect is determined by the balance between the progression of underlying atherosclerosis and the formation of new blood vessels. The reduction in anginal complaints and the improvement in quality of life, lasting for at least 12 months[2], can be considered an important relief for these patients. Therefore, it may be proposed to perform a repeat bone marrow cell injection in selected patients with recurrent anginal complaints, aiming to renew neovascularization and relief of anginal complaints.

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