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Bone Marrow-Derived Cell Therapy After Myocardial Infarction

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We would like to clarify several points in the editorial (1) accompanying our publication of the TIME report (2).

First, the automated system for extracting bone marrow-derived mononuclear cells (MNCs) used for Cardiovascular Cell Therapy Research Network (CCTRn) clinical trials (2,3,4) employs Ficoll gradient centrifugation, similar to the manual method used for REPAIR AMI (5). Thus, the difference lies in improved reproducibility and standardization by the automated system, not some other fundamental characteristic.

Second, our original publication erroneously listed the heparin concentration at 0.1 units/ml. In fact, no heparin was added to the automated system, and cells used in all CCTRn studies contained only residual heparin from bone marrow aspiration, estimated to be not more than 0.01 units per ml (Data Correction 6). This is five times below the lowest concentration evaluated (7) in a stromal cell-derived factor-1- (SDF-1)-stimulated invasion capacity assay, and 200-2000 times lower than heparin concentrations used in other functional assays reported by this group. Accordingly, the statement: "... the cell product used in TIME contained heparin at a dose that has been shown to impair the migratory capacity of MNCs" is no longer supported by the facts. We regret the confusion caused by our error.

Third, the statement, "MNCs isolated by the automated system used in this study have not been tested in an animal model of MI, and cell bioactivity has not been verified in any human studies of heart disease" should be considered in view of the following: (a) MNCs from automated and manual preparations were found to have similar reperfusion activity in a murine hind-limb ischemia model (2); (b) A Cochrane review of stem cell studies (8) reported ten clinical trials cells were administered in a solution of "standard saline containing heparin." Of these ten studies, we note that seven disclosed positive results (e.g., increased left ventricular ejection fraction, LVEF);(c) in the CCTRn FOCUS trial we found that LVEF increased 2.7% in patients receiving MNCs versus placebo, and that this increase was associated with higher percentages of CD34+ and CD133+ MNCs (3). Additionally, pre-clinical studies by CCTRn investigators demonstrated retention of SDF-1 migration and CFU-activity when MNCs isolated by the automated system were compared with MNCs from the manual method (unpublished observations). Thus, cell bioactivity was observed not only in one CCTRn trial (with miniscule residual heparin) but also in seven other trials in which cells were re-suspended in heparin. One explanation for this retention of bioactivity is that "...the effects of heparin can be ameliorated by excessive serum in vitro..." (7).

Summarizing, the available evidence does not support the contention that bioactivity of cells administered in the TIME study was impaired by processing techniques or exposure to heparin. We believe that the TIME results are consistent with a limited effect of bone marrow cells on recovery of LV function, and support previous findings (9) demonstrating that MNCs have reduced cytokine and growth factor production compared to other bone marrow-derived stem and progenitor cells.

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