Feasibility and Safety of Intra-Coronary Bone Marrow Mononuclear Cell Transplantation in ST Elevation Myocardial Infarction Patients

Suphot Srimahachota MD*,
Smonporn Boonyaratavej MD*, Pairoj Rerkpattanapipat MD**,
Somjai Wangsupachart MD**, Monravee Tumkosit MD**,
Udomsak Bunworasate MD***, Thayapong Na Nakorn MD***,
Tanin Intragumtornchai MD***, Pawinee Kupatawintu RN*****,
Sunisa Pongam RN*, Aem-orn Saengsiri RN*,
Mantana Pothisri RN**, Yeesoon Sukseri RN*,
Tanorm Bunprasert MD****, Taworn Suithichaiyakul MD*

** Division of Cardiology, Department of Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand*
*** Department of Radiology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand*
**** Division of Hematology, Department of Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand*
***** Department of Ear Nose Throat, King Chulalongkorn Memorial Hospital, BAngkok, Thailand*
****** Blood Bank, Thai Red Cross Society, Bangkok, Thailand*

Background: *Stem cell transplantation is a potential treatment to improve left ventricular ejection fraction (LVEF) after ST elevation myocardial infarction (STEMI). However, technique and mode of transplantation, type of cells, number of cells, and when to transplant are still unknown.*
Objective: *To determine the feasibility and safety of bone marrow mononuclear cell (BMC) intra-coronary transplantation and 6-months results in patients with STEMI.*
Material and Method: *After successful percutaneous coronary intervention (PCI) in STEMI patients who did not have flow re-established within 12 hours and poor LVEF (less than 50%) by echocardiography were enrolled. Bone marrow aspiration of 100 cc was performed in the morning. After cell processing for 3 hours, the suspension of BMC about 10 cc were infused to infarcted area using standard PCI technique. Balloon occlusion for 3 minutes was performed during cell infusion. Cardiac magnetic resonance imaging was used to determine LVEF, scar volume and LV volume before and 6 months after transplantation.*
Results: *Five patients were enrolled between May and August 2006. Duration of STEMI before transplantation ranged from 18 days to 14 years. Total amount of BMC ranged from 67 x 10^6 to 335 x 10^6. Number of CD 34^+ and CD 133^+ cells were approximation to be 0.7 x 10^6 to 7.7 x 10^6 and 0.01 x 10^6 to 3.04 x 10^6. LVEF was increased from 36.4 at baseline to 43.3 at 6-month. NT pro-BNP level was decreased from 1105 ng/ml at baseline to 288 pg/ml at 6-month. No complications such as chest pain, no re-flow phenomenon, ventricular arrhythmia, or hypotension was detected during the procedure.*
Conclusion: *Intra-coronary BMC transplantation in patients with STEMI in our center is feasible and safe. LVEF was slightly improved; however, a randomized controlled study is needed.*

Keywords: *Intracoronary, Bone marrow mononuclear cell transplantation, ST elevation myocardial infarction*

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Correspondence to: Srimahachota S, Division of Cardiovascular Diseases, Department of Medicine, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand. Phone: 0-2256-4291, Fax: 0-2256-4291, E-mail: s_srimahachota@yahoo.co.th

Acute ST-elevation myocardial infarction (STEMI) is a serious condition leading to high in-hospital as well as long-term mortality[1-5]. Left ventricular (LV) dysfunction due to myocardial necrosis is one of the poor prognostic indicators after STEMI. Because of the advance of stem cell knowledge, many reports implanted stem cells into the heart muscle either via intra-coronary or direct injection for myocardial regeneration[6-18]. Some of these trials demonstrated improvement of LV ejection fraction (EF) whereas many did not. Because of different techniques, different cell type, different inclusion criteria or different method of evaluation, the outcomes may be different. The present study was conducted to determine the safety and feasibility of the authors' technique for intra-coronary bone marrow mononuclear cell (BMC) transplantation in STEMI patients who failed to receive reperfusion with 12 hours of onset of chest pain.

Material and Method

Five patients who had a history of STEMI and did not receive any reperfusion within 12 hours were enrolled. The LVEF had to be less than 50% with regional wall motion abnormality by echocardiography. The patients had to have successful angioplasty with or without stent implantation for infarct related artery. Echocardiography and cardiac magnetic resonance imaging (CMR) were performed for evaluation of LVEF and regional wall motion abnormality prior to stem cell, 3 and 6 months after BMC transplantation. Coronary angiography (CAG) and LV angiography were performed before and 6 months after transplantation. The authors excluded the patients who had cardiogenic shock, severe congestive heart failure (function class 4), impaired renal function (creatinine > 1.8 mg/dl), pregnancy, and other severe co-morbid disease with life expectancy less than 1 year. All patients had to sign informed consent prior enrollment. The present study was approved by the ethics committee of the Faculty of Medicine, Chulalongkorn University.

BMC preparation

Fifty ml of bone marrow from iliac crest was harvested in the morning under local anesthesia with conscious sedation and sent immediately to cell-processing laboratory at National Blood Centre, the Thai Red Cross Society. Mononuclear cells were isolated by density gradient centrifugation (Isoprep®). After 2 washing steps with saline + 2% autologous serum, cells were suspended in 10 ml of saline + 2% autologous serum. Cells population including total mononuclear cells, $CD34^+$ cells and $CD133^+$ cells were analyzed using flow cytometer as well as the cell viability study before transplantation. After the first case of cell analysis, the authors found that the total mononuclear cells was much smaller than the previous study[7], then 100 ml of bone marrow was used instead of 50 ml.

Cell transplantation technique

Standard percutaneous coronary intervention (PCI) procedure was performed to transplant BMC immediately after cell processing. Over-the-wire balloon was inflated in the infarct related artery to stop-flow and then slowly infused 3.3 ml of cell suspension through the wire lumen into the infarcted area followed by balloon occlusion for 3 minutes. Cells infusion was repeated three times. Coronary angiography was done before finishing the procedure.

Results

Between May and August 2006, 5 ST elevation MI patients who did not receive reperfusion within 12 hours of onset of chest pain and successful PCI with stent in the infarct related artery were enrolled. The baseline characteristics are shown in Table 1. Duration of myocardial infarction prior to cell transplantation varied from 18 days to 14 years. Average LV EF using CMR was 36.4. One patient had screening LVEF of less than 50 when using echocardiography but when CMR was performed, the LVEF was more than 50. Total BMC after processing was 67-335 x 10^6 cells with average cells viability were over 90%. Six months outcomes after cell transplantation are shown in Table 2. All of the patients had improved their function class to class I as well as the level of NT pro-BNP, biomarker for congestive heart failure. Average LVEF by CMR was improved from 36.4 to 43.3 at 6-months and to 44.2 at the end of 1-year post transplantation (Fig. 1). However, the LV end systolic volume, LV end diastolic volume, LV scar volume, and percent of scar to LV volume at 6-months did not change much when compared with the previous treatment with BMC. During cells transplantation, no complications such as chest pain, no re-flow phenomenon, ventricular arrhythmia, or hypotension were detected during the procedure

Discussion

This is the feasibility and safety study for intra-coronary BMC transplantation in our center and

Table 1. Baseline characteristics of the patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (year)	62	47	45	62	68
Sex	Male	Male	Male	Male	Female
Duration of MI	14 y	50 d	18 d	70 d	36 d
Area of MI	Anterior	Anterior	Anterior	Anterior	Anterior
NYHA-FC	II	II	III	II	III
LVEF by CMR	26.0	26.7	47.4	29.0	53.0
LV scar volume (ml)	57.9	45.6	22.3	55.0	42.5
BM volume (ml)	50	100	100	100	100
Total mononuclear cell (x10^6 cells)	67	176	311	318	335
$CD34^+$ (%)	1.16	1.58	1.81	1.73	2.32
$CD133^+$ (%)	0.02	0.72	0.43	0.72	0.91
Cell viability (%)	97	93	87	97	98

MI = myocardial infarction, NYHA-FC = New York Heart Association functional class, LVEF = left ventricular ejection fraction, CMR = cardiac magnetic resonance imaging, BM = bone marrow

Table 2. Outcomes of the patients after bone marrow mononuclear cells transplantation

	Case 1	Case 2	Case 3	Case 4	Case 5	Average
NYHA-FC						
Pre	II	II	III	II	III	2.4
6 month	I	I	I	I	I	1
LVEF by CMR						
Pre	26.0	26.7	47.4	29.0	53.0	36.4
6 month	28	34	61	38	56.5	43.3
LVESV (ml)						
Pre	170	155	72	166	79	128
6 month	170	143	43	132	77	113
LVEDV (ml)						
Pre	239	211	137	234	168	198
6 month	237	217	112	214	171	190
Scar volume (%)						
Pre	57.9	45.6	22.3	55.0	42.5	44.7
6 month	58.7	55.5	19.0	54.5	27.9	43.1
Scar/LV (%)						
Pre	31.7	28.0	20.0	30.3	29.2	27.8
6 month	34.0	39.0	16.0	24.5	15.8	25.9
NT pro-BNP (pg/ml)						
Pre	378	1,737	634	1,055	1,722	1,105
6 month	157	474	110	288	1,125	431

NYHA-FC = New York Heart Association functional class, LVEF = left ventricular ejection fraction, CMR = cardiac magnetic resonance imaging, LVESV = left ventricular end systolic volume, LVEDV = left ventricular end diastolic volume

shows that it could be safely performed. It was better to harvest 100 ml of bone marrow instead of 50 ml in terms of increasing total amount of BMC. Cell viability after processing was achieved more than 90% in the present study. Using a flow cytometer, only a small percent of endothelial progenitor cell (EPC) such as $CD34^+$ and $CD133^+$ cell were detected. LVEF was improved in about 7% points at 6-months

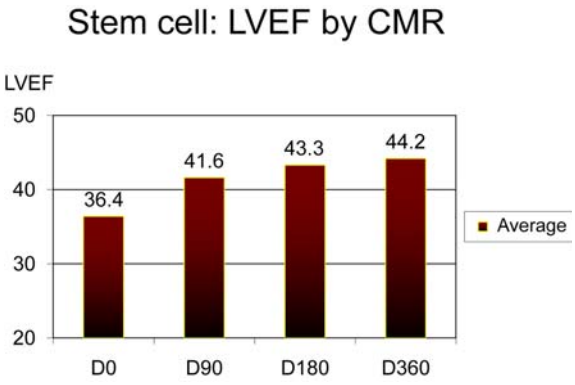

Fig. 1 Average left ventricular ejection fraction using cardiac magnetic resonance imaging at pre, day 90, d180 and d360 after cell transplantation

post transplantation as in the previous reports[6-8]. However, LVESV, LVEDV, LV scar volume, and percent scar to LV volume did not have change much from the pre-treatment. The functional class and NT pro-BNP are significantly improved at 6-months of follow-up. Nevertheless, this improvement may be due to the successful opening of the infarct-related vessel as well as receiving the standard treatment for myocardial infarction of the patients. A randomized controlled trial with a larger sample size is needed.

Conclusion

Intra-coronary BMC transplantation in patients with STEMI in our center is feasible and safe. The NYHA-FC, biomarker for heart failure-NT pro-BNP and LVEF were improved. However, a randomized controlled study with a larger sample size is needed.

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การศึกษาความเป็นไปได้และความปลอดภัยของการรักษาผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลันชนิด ST-elevation โดยการใช้ bone marrow mononuclear cell ฉีดเข้าในหลอดเลือดหัวใจ

สุพจน์ ศรีมหาโชตะ, สมนพร บุณยะรัตเวช, ไพโรจน์ พฤกษ์พัฒนาพิพัฒน์, สมใจ วังศุภชาติ, มนรวีร์ ทุมโฆษิต, อุดมศักดิ์ บุญวรเศรษฐ์, ธัญญพงษ์ ณ นคร, ธานินทร์ อินทรกำธรชัย, ภาวิณี คุปตวินธุ, สุนิสา โพธิ์งาม, เอมอร แสงศิริ, มัณนา โพธิ์ศรี, ยี่สุ่น สุขเสรี, ถนอม บรรณประเสริฐ, ถาวร สุทธิไชยากุล

ภูมิหลัง: *การใช้เซลล์ต้นกำเนิดเป็นความหวังในการรักษาผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลันชนิด ST elevation ที่มีการทำงานของหัวใจลดลง อย่างไรก็ตาม วิธีการ ชนิดของเซลล์ต้นกำเนิด จำนวน รวมทั้งระยะเวลาที่จะให้เซลล์ยังไม่เป็นที่ตกลงกันแน่ชัด*

วัตถุประสงค์: *เพื่อศึกษาความเป็นไปได้และความปลอดภัยในการใช้ bone marrow mononuclear cell (BMC) ฉีดเข้าในหลอดเลือดหัวใจในผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลันชนิด ST-elevation*

วัสดุและวิธีการ: *หลังจากที่ทำบอลลูนขยายหลอดเลือดในผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลันชนิด ST elevation ที่ไม่ได้รับการทำ reperfusion ภายใน 12 ชั่วโมงและมีการทำงานของหัวใจน้อยกว่า 50% เข้าการศึกษา ผู้ป่วยจะได้รับการเจาะไขกระดูกจำนวน 100 มล.ในตอนเช้า และส่งไปทำการแยก mononuclear cell โดยใช้เวลา 3 ชั่วโมง ซึ่งจะได้ของเหลวที่มีเซลล์ปริมาตร 10 มล. เพื่อที่จะฉีดเข้าหลอดเลือดหัวใจ โดยใช้วิธีการปกติของการทำบอลลูนขยายหลอดเลือด ขณะที่ฉีดเซลล์เข้าสู่กล้ามเนื้อหัวใจ บอลลูนจะถูกขยายออกเป็นเวลา 3 นาที การทำงานของหัวใจ ปริมาณของกล้ามเนื้อที่ตาย จะตรวจโดยการใช้คลื่นแม่เหล็ก โดยเปรียบเทียบก่อนทำและที่ 6 เดือนหลังจากทำการฉีดเซลล์ต้นกำเนิด*

ผลการศึกษา: *จากพฤษภาคมถึงสิงหาคม พ.ศ. 2549 ผู้ป่วยจำนวน 5 ราย โดยมีระยะเวลาที่เกิดกล้ามเนื้อหัวใจตายเฉียบพลันจนถึงได้รับการรักษาด้วยเซลล์ต้นกำเนิด 18 วัน ถึง 14 ปี จำนวนเซลล์ที่ได้อยู่ระหว่าง 67-335 ล้านเซลล์ โดยมีเซลล์ $CD34^+$ และ $CD133^+$ อยู่ที่ 0.7-7.7 ล้านเซลล์และ 0.01-3.04 ล้านเซลล์ตามลำดับ LVEF เพิ่มขึ้นจาก 36.4 เป็น 43.3 และ ระดับ NT pro-BNP ลดลงจาก 1105 pg/ml เป็น 431 pg/ml ที่ 6 เดือน ไม่พบภาวะแทรกซ้อน เช่น อาการเจ็บหน้าอก การอุดตันของหลอดเลือดหัวใจ ภาวะหัวใจเต้นผิดจังหวะ หรือ ความดันต่ำเกิดขึ้นขณะที่ทำการฉีดเซลล์ต้นกำเนิด*

สรุป: *การใช้ BMC ในการฉีดเข้าหลอดเลือดหัวใจในผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลันชนิด ST-elevation สามารถทำได้และมีความปลอดภัย และทำให้การทำงานของหัวใจดีขึ้น แต่อย่างไรก็ตาม จำเป็นต้องมีการศึกษาต่อไปโดยกลุ่มควบคุมเพื่อเป็นการเปรียบเทียบ*