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SHORT COMMUNICATION

Use of adipose-derived stromal cells in the treatment of chronic ischaemic heart disease: safety and feasibility study

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INTRODUCTION

Ischaemic heart diseases and cerebrovascular diseases cause the highest number of deaths among the Polish population. Despite constant advances in treatment options, symptoms caused by obstructed arterioles and capillaries may be difficult to alleviate, especially because heavily calcified arteries may not qualify for interventional procedures [1].

On the other hand, formation of new blood vessels is a complex and integrated process. In angiogenesis, new microvessels are generated from preexisting vasculature by the proliferation and migration of endothelial cells [2]. This process is regulated by growth factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor (TGF), and angiopoietin-1.

Mesenchymal stem cells (MSCs) are a heterogeneous population of fibroblast-like multipotent cells that can differentiate into various mesodermal lineages, such as adipocytes, chondrocytes, or cardiomyocytes. Many preclinical cardiovascular regenerative studies demonstrated that MSCs can alleviate cardiac insult and promote recovery in large animal models [3]. The most widely investigated stem cells for the treatment of heart failure or ischaemic heart disease are bone marrow-derived mesenchymal stromal cells.

Adipose-derived stromal cells (ADSCs), which are proposed as a treatment option in this study, present similar cell characteristics to bone marrow stem cells. Nevertheless, they show a higher stem cell proliferation potential with greater yield of pluripotent stem cells [4].

On the other hand, based on animal experiments, neoangiogenesis and tissue perfusion may be stimulated by transmyocardial revascularisation because it induces a highly disorganised pattern of neovascularisation at the periphery in a nonspecific response similar to that observed in scar tissue [5].

Therefore, based on promising results from in vitro and animal studies, we delivered fresh ADSCs intramyocardially, with use of a medical laser, to patients with chronic ischaemic heart disease who did not qualify for standard methods of treatment (percutaneous coronary intervention, coronary artery bypass grafting).

METHODS

A total of 15 patients with refractory angina (Canadian Cardiovascular Society class II or greater), who were disqualified from direct myocardial revascularisation based on the decision of the Heart Team, were enrolled in the study. Other inclusion criteria comprised left ventricular ejection fraction (LVEF) greater than 20%, impaired endocardial movement and myocardial thickening at the anterior heart wall, and the absence of transmural scar at the anterior heart wall, based

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Table 1. Baseline characteristics and perioperative results

Baseline characteristics	Analysed population (n = 15)
Chronic ischaemic heart disease	15 (100%)
Age [years]	65 (55–74)
Body mass index [kg/m^2]	29.8 (24–42)
BSA women [m^2]	1.7 (1.5–1.9)
BSA men [m^2]	1.93 (1.7–2.2)
Prior MI	12 (8%)
Hypertension	14 (93%)
Diabetes	5 (33%)
Prior PCI	5 (33%)
Prior CABG	3 (20%)
Hypercholesterolaemia	13 (87%)
Peripheral artery disease	5 (33%)
CCS class II	5 (33%)
CCS class III or IV	10 (67%)
Left anterior descending artery:	
Chronic total occlusion	9 (60%)
Significant stenosis (75–99% stenosis)	6 (40%)
CMR baseline results:	
LVEDV/BSA [mL/m^2]	135 (96.1–213)
LVESV/BSA [mL/m^2]	91 (45.8–169)
LVSV [mL]	80.5 ± 8.1
LVM/BSA women [g/m^2]	86
LVM/BSA men [g/m^2]	104
LVEF [%]	36 (20–52)
Periprocedural outcomes:	
Mean procedure duration [min]	179
Amount of harvested fat tissue [mL]	220 (120–360)
Cardiovascular complications (MI, death, haemodynamic instability)	0 (0%)
Malignant arrhythmia	0 (0%)
Harvest side complications (bleeding, infections)	0 (0%)
30-days outcomes:	
Major adverse cardiac event	0 (0%)
Readmission due to cardiac causes	0 (0%)

Data shown as mean ± standard deviation or as median (interquartile range), or number (percentage). BSA — body surface area; CABG — coronary artery bypass grafting; CMR — cardiac magnetic resonance; CCS — Canadian Cardiovascular Society; LVM — left ventricular mass; LVEDV — left ventricular end-diastolic volume; LVEF — left ventricular ejection fraction; LVESV — left ventricular end-systolic volume; LVSV — left ventricular systolic volume; MI — myocardial infarction; PCI — percutaneous coronary intervention

on cardiac magnetic resonance examination (Table 1). The study was approved by the Bioethics Committee. All patients gave written consent to participate.

During the procedure, fat tissue was collected from the abdominal area under general anaesthesia, similarly to standard liposuction procedure. The harvested tissue was purified using a Celution 800/CRS® System (Cytori Therapeutics, San Diego, CA, USA), to obtain a 5-mL suspension of ADSCs.

The average number of implanted stem cells was 40×10^6. For cell purification we used dedicated medical equipment that enabled reliable and reproducible isolation of adipose-derived stromal cells from fat tissue [6]. ADSCs were implanted immediately to the same patient from whom they were obtained, simultaneously with myocardial laser revascularisation (Holmium:YAG laser) via left-sided mini-thoracotomy. During the procedure, five channels were created using low power (7 W), and around 1 mL of cell suspension was implanted for each channel with the use of a PHOENIX combined delivery system (CryoLife, Kennesaw, GA, USA).

RESULTS AND DISCUSSION

Overall, 15 patients aged from 55 to 74 years (mean age 65 years) were enrolled, including 12 (80%) patients after myocardial injury. Mean LVEF was 36%, which was caused by myocyte destruction due to ischaemia.

The proposed procedure is a feasible treatment option that may be performed safely in an experienced cardiac centre. The mean operative time was 179 min and adipose tissue was successfully harvested from all patients. We were able to follow the study protocol in all of the cases and there were no perioperative complications or significant changes in laboratory parameters from baseline levels observed. Moreover, the mean blood loss during the procedure was 70 mL and patients were discharged home on postoperative day 7.

At the 30-day follow-up, we did not observe any major adverse cardiac or cerebrovascular events. During this period, patients did not require readmission due to cardiac causes.

Inclusion criteria ensured enrolment only of patients with confirmed eccentric left ventricular (LV) hypertrophy and LV systolic dysfunction due to ischaemia. Loss of active myocytes resulted in increased LV diastolic volume and consequently LV diastolic blood pressure, which was observed. Because LV pressure overload, along with neurohormonal changes, induces eccentric hypertrophy, all patients had hypokinesis or akinesis, impaired endocardial movement, and myocardial thickening at the anterior wall.

Nevertheless, the success of cell-based therapies depends on whether the engrafted cells differentiate into functional vascular cells and whether those cells can produce paracrine signals that encourage survival of the cells in the ischaemic environment [2].

Adipose-derived stromal cells are increasingly used in stem cell research. Freshly isolated ADSCs are known to be heterogeneous and contain haematopoietic cells (CD45+ and/or CD34+) and vascular endothelial cells (CD34+/CD31+) in addition to stem cells (CD44+ and CD105+).

Schenke-Layland et al. [7] showed that the ADSC-treated group presented lower LV end-diastolic dimension, and significantly improved LVEF and cardiac output [7]. Rehman et al. [8] examined the production of paracrine factors by human ADSCs and showed that ADSCs produce VEGF, bFGF, and TGF-β. The paracrine effect of transplanted stem cells has been emphasised recently.

The aim of ADSC implantation in patients with chronic ischaemic heart disease was to initiate angiogenesis in ischaemic myocardium, which would slow down the process of adverse LV remodelling and heart failure development.

In particular, the paracrine effect from transplanted ADSCs may play a major role in this process. Administered mesenchymal stromal cells were fresh and co-administered with stromal vascular fraction, which may also be involved in stem cell activation.

Left sided mini-thoracotomy is a safe and proven method to gain access to the anterior heart wall and allows ADSC implantation at the scheduled area of the heart muscle. There were no difficulties with the identification of the administration site or with the process of implantation.

To intensify the process of mesenchymal stromal cell activation, we used a medical laser. Around the channel formed by the laser, a special "border zone" was created. The cytokines released in this area probably serve as a "homing" signal for circulating stem cells, particularly endothelial progenitor cells.

Animal experiments suggest that transmyocardial revascularisation induces a highly disorganised pattern of neovascularisation at the periphery in a nonspecific response similar to that observed in scar tissue. Atluri et al. [5] also revealed significant increases in angiogenesis and perfusion.

An important part of any study using innovative therapeutic methods is to ensure patient safety. It should be emphasised that during the procedures there were no complications and patients were discharged home in good general condition.

During the 30-day follow-up, no patient required hospitalisation for heart disease. The patients did not report exacerbation of symptoms of angina pectoris. The final effect of the applied innovative therapy will be evaluated at 12 months post-surgery.

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Conflict of interest: *none declared*

References

1. Tomasiewicz B, Ferenc M, Zimoch W, et al. Left ventricle assist device supported rotational atherectomy of the highly calcified last remaining vessel in a patient with acute myocardial infarction and reduced left ventricular function. Kardiol Pol. 2016; 74(12): 1508, doi: 10.5603/KP.2016.0176, indexed in Pubmed: 28009041.
2. Szöke K, Brinchmann JE. Concise review: therapeutic potential of adipose tissue-derived angiogenic cells. Stem Cells Transl Med. 2012; 1(9): 658–667, doi: 10.5966/sctm.2012-0069, indexed in Pubmed: 23197872.
3. Yu H, Lu K, Zhu J, et al. Stem cell therapy for ischemic heart diseases. Br Med Bull. 2017; 121(1): 135–154, doi: 10.1093/bmb/ldw059, indexed in Pubmed: 28164211.
4. Zhu Y, Liu T, Song K, et al. Adipose-derived stem cell: a better stem cell than BMSC. Cell Biochem Funct. 2008; 26(6): 664–675, doi: 10.1002/cbf.1488, indexed in Pubmed: 18636461.
5. Atluri P, Panlilio CM, Liao GP, et al. Transmyocardial revascularization to enhance myocardial vasculogenesis and hemodynamic function. J Thorac Cardiovasc Surg. 2008; 135(2): 283–91, 291.e1; discussion 291, doi: 10.1016/j.jtcvs.2007.09.043, indexed in Pubmed: 18242252.
6. Fraser JK, Hicok KC, Shanahan R, et al. The celutionsystem: automated processing of adipose-derived regenerative cells in a functionally closed system. Adv Wound Care (New Rochelle). 2014; 3(1): 38–45, doi: 10.1089/wound.2012.0408, indexed in Pubmed: 24761343.
7. Schenke-Layland K, Strem BM, Jordan MC, et al. Adipose tissue-derived cells improve cardiac function following myocardial infarction. J Surg Res. 2009; 153(2): 217–223, doi: 10.1016/j.jss.2008.03.019, indexed in Pubmed: 18694573.
8. Rehman J, Traktuev D, Li J, et al. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. Circulation. 2004; 109(10): 1292–1298, doi: 10.1161/01.CIR.0000121425.42966.F1, indexed in Pubmed: 14993122.

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