Journal of Translational Medicine

RESEARCH

Open Access

Safety and therapeutic potential of allogeneic adipose-derived stem cell spray transplantation in ischemic cardiomyopathy: a phase I clinical trial

Takuji Kawamura[1], Daisuke Yoshioka[1], Ai Kawamura[1], Yusuke Misumi[1], Takura Taguchi[1], Daisuke Mori[1], Shunsuke Saito[1], Takashi Yamauchi[1], Hiroki Hata[1] and Shigeru Miyagawa[1*]

Abstract

Background Ischemic cardiomyopathy, characterized by coronary artery atherosclerosis, impairs the myocardial tissue. Coronary artery bypass grafting (CABG) is commonly used to revascularize affected areas and improve patient survival rates; however, it can fail to enhance cardiac function. Impaired capillary blood flow may obstruct functional recovery, prompting interest in treatments, such as angiogenic factor administration. Adipose-derived stem cells (ADSCs), which are known for immune evasion, have shown the potential to construct capillary networks and improve myocardial function. This clinical trial aimed to evaluate the safety and efficacy of ADSC spray therapy combined with CABG.

Methods This single-center, randomized, double-blind study involved patients with ischemic cardiomyopathy who were scheduled for CABG and who had a left ventricular ejection fraction ≤ 40%. The participants were randomized to receive CABG as well as ADSC spray therapy or placebo. The primary endpoints were safety, changes in late gadolinium-enhanced (LGE) magnetic resonance imaging (MRI) volumes, and feasibility. The secondary endpoints included left ventricular function, exercise tolerance, and heart failure symptoms.

Results Seven patients were enrolled; of them, six were randomized to receive ADSC therapy (n = 3) or placebo (n = 3). The procedure was successfully completed with minimal adverse events. One patient in the ADSC group developed pleural effusion that was resolved with drainage. The LGE-MRI volumes decreased in the ADSC group but remained unchanged in the placebo group. Improvements in left ventricular function and exercise tolerance were noted in the ADSC group, with heart failure symptoms improving to New York Heart Association class I. In contrast, the placebo group showed no significant changes, with one patient experiencing worsening symptoms.

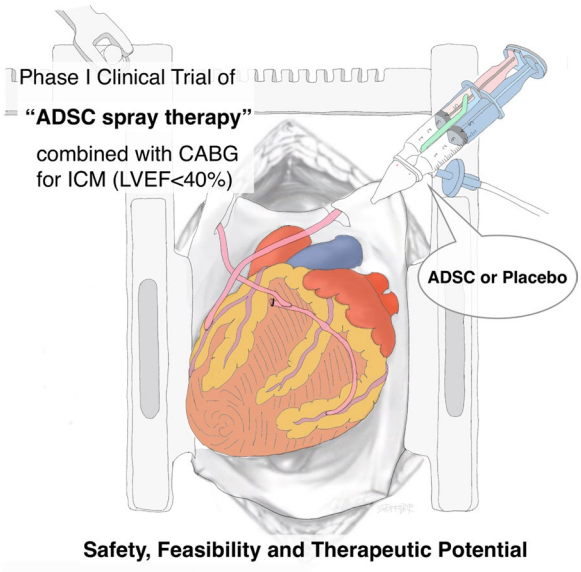
Conclusions ADSC spray therapy combined with CABG demonstrated safety and efficacy at enhancing cardiac function. ADSC likely contributes to capillary network reconstruction, thereby augmenting the benefits of CABG. Future phase II and III trials are warranted to confirm its therapeutic efficacy and long-term outcomes. This novel approach represents a significant advancement in the treatment of ischemic cardiomyopathy and offers a viable strategy for improving myocardial function and patient prognosis.

Trial registration This study was registered with the Japan Registry of Clinical Trials (jRCT2053190103) and ClinicalTrials.gov (NCT04695522)

Keywords Cell therapy, Adipose-derived mesenchymal stem cells, Myocardial regenerative medicine, Heart failure, Coronary artery bypass grafting

*Correspondence:
Shigeru Miyagawa
miya-p@surg1.med.osaka-u.ac.jp

Graphical Abstract



Background

Ischemic cardiomyopathy is characterized by an imbalance between myocardial blood supply and demand due to coronary artery atherosclerosis and leads to functional impairment of the myocardial tissue [1] ranging from severe (myocardial necrosis) to intermediate (functional decline due to blood flow imbalance) cases. The term "hibernating myocardium" implies that functional improvement is attainable through revascularization [2, 3]. Coronary artery bypass surgery (CABG), a widely accepted method for revascularization in patients with ischemic cardiomyopathy, has the potential to increase long-term survival [4]. However, there have been no reports of significant enhancement in cardiac function after CABG [5], highlighting the need for additional interventions. Because impaired capillary blood flow may hinder cardiac function, reconstruction of the capillary network may activate the hibernating myocardium and enhance cardiac function. Therefore, novel therapeutic interventions, such as the administration of angiogenic factors or cells that produce angiogenic factors, have been investigated [6].

Adipose-derived stem cells (ADSCs) are mesenchymal stem cells isolated from adipose tissue that function as a versatile cell source for clinical applications because their immune evasion ability allows their transplantation from allogeneic donors [7]. To date, clinical trials such as the SCIENCE trial, in which ADSCs were injected intramyocardially via a catheter, have been conducted to confirm their safety; however, no improvements in therapeutic efficacy have been reported [8]. We previously published extensive studies of the basic and preclinical aspects of allogeneic ADSCs [9–12]. We have suggested "cell spray therapy," in which cells suspended in fibrin glue are directly sprayed onto the heart perioperatively to improve cardiac function in cases of ischemic cardiomyopathy [12]. This approach demonstrated the construction of capillaries through angiogenic factors and the functional improvement of the hibernating myocardium as key mechanisms. This study explored the safety and therapeutic effects of ADSC spray therapy combined with CABG to determine its clinical viability for treating ischemic cardiomyopathy.

Methods

Study design

This was an investigator-initiated single-center, randomized, parallel-group, double-blind clinical trial. Patients were randomized in a 1:1 ratio to receive the test product (ADSC group) or placebo (placebo group). The primary endpoints included: (1) product-related adverse events and safety assessment; (2) changes in late gadolinium-enhanced (LGE) magnetic resonance imaging (MRI) volume from screening to 24 weeks post-procedure; and (3) feasibility. The secondary endpoints were (1) changes in left ventricular function; (2) changes in exercise tolerance; and (3) changes in heart failure severity and symptoms.

The selection of LGE-MRI volume as a primary endpoint was motivated by the understanding that the general evaluation of cardiac function, such as left ventricular wall motion, may be enhanced by coronary artery bypass grafting (CABG) alone, which may not adequately reflect the impact of cell therapy. Previous reports indicated that LGE-MRI volume remained unchanged with CABG alone but decreased when CABG was combined with cell therapy [13, 14]. Considering the correlation between LGE-MRI volume and prognosis after CABG for ischemic cardiomyopathy [15], the LGE-MRI volume was deemed crucial in examining prognostic improvement through cell therapy in this trial.

Inclusion criteria

Patients who met the following criteria were included: (1) diagnosis of ischemic cardiomyopathy treated with coronary artery bypass surgery; (2) left ventricular ejection fraction (LVEF) $\leq$ 40% based on echocardiography within 4 weeks before study consent; (3) congestive heart failure, even if treated with guideline-directed medical therapy; and (4) aged 20–80 years at the time of study consent.

Exclusion criteria

Patients who met any of the following criteria were excluded: (1) severe valvular or cardiovascular abnormalities affecting trial procedures; (2) acute myocardial infarction within 2 weeks prior to consent; (3) history of alcoholism or drug addiction within 6 months before registration; (4) severe psychosis or psychiatric symptoms hindering trial participation; (5) diagnosis of malignant tumors within 5 years prior to consent; (6) confirmed or possible pregnancy; (7) refusal of blood transfusion; (8) hypersensitivity to fibrinogen and thrombin products; (9) active infections; (10) participation in other clinical trials within 180 days; (11) contraindications to MRI, e.g., non-MRI-compatible pacemaker implants; (12) renal dysfunction (chronic kidney disease stage D or worse) and hepatic dysfunction (Child–Pugh B or C); and (13) deemed inappropriate for the study by an investigator.

Preparation of human ADSCs

Cell suspensions containing human ADSCs (ADR-002K) extracted from adipose tissue and cryopreserved after culturing were obtained from Rohto Pharmaceutical Co., Ltd. Information on ADSCs authorized for disclosure by Rohto Pharmaceutical Co., Ltd. included the presence of positive markers and the absence of negative markers as previously defined by the International Society for Cell Therapy [16]; confirmed fat, bone, and chondrogenic differentiation potential; and confirmed sterility, mycoplasma negativity, and virus negativity tests.

The preparation used to mix and spray ADSCs in fibrin glue was performed using clinically available solutions according to the procedure described previously [12]. First, the cell suspensions were lysed in a 37 °C thermostatic bath and then suspended to 1×10^8 ADSCs/mL to prepare the ADSC suspensions. Solutions A (containing fibrinogen) and B (containing thrombin) were purchased from BOLHEAL (KM Biologics Co.). Fibrin glue was prepared as previously described. Two milliliters of Solution B was mixed with 3 mL of the ADSC suspension, while 5 mL of Solution B containing 3×10^8 ADSCs was collected in the syringe of the spray set. Two milliliters of Solution A and 3 mL of the starting solution were mixed and collected using the syringe of the spray set. To ensure double-blindness, the spray set was prepared on a clean bench in a room separate from the operating room by personnel not associated with the surgery, and the syringe used to collect the cell suspension was covered with a colored drape so that its contents could not be identified. The ADSC suspension was administered to the patient in the operating field within 30 min of mixing.

Surgical procedure

CABG and cell spray transplantation of ADSCs or placebo were performed via median sternotomy. The detailed CABG procedure, including the target vessels, graft design, and need for cardiopulmonary bypass, was determined preoperatively after discussion among the heart team based on the policy of complete revascularization and bypass using arterial grafts, with the same indications as those for normal CABG. The cell spray transplantation of ADSCs was performed as described previously [12] after the CABG procedure and immediately before the chest closure. Spray sets of fibrin glue containing ADSCs or placebo, prepared as described above, were sprayed and transplanted onto the surface of the left ventricle using CO_2 gas. The area where the cells were transplanted using the spray method was identified as an ischemic lesion during the preoperative examination.

Medication therapy

Regarding cardioprotective drugs, types and doses of preoperative medication should usually be restarted as soon as possible after the patient resumes postoperative oral intake.

Data collection

The patients' preoperative characteristics were recorded during a 4-week screening process. Postoperatively, adverse events and changes in LGE-MRI volume, cardiac

function evaluated by cardiac computed tomography CCT or echo, exercise tolerance via a 6-min walk test, heart failure symptoms (New York Heart Association [NYHA] Functional Classification), Minnesota Living with Heart Failure Questionnaire (MLHFQ), and *N*-terminal pro-brain natriuretic peptide (NT-proBNP) measurements were assessed until 24 weeks postoperative. Independent clinical trial coordinators collected the data for analysis at an external data center.

Statistical analysis

This phase I trial involved six patients with a focus on safety confirmation. Owing to the concurrent impact of CABG, a statistical analysis of the therapeutic effects of ADSCs versus placebo was omitted. Missing data were analyzed without additional processing.

Results

Seven patients who met the inclusion criteria were enrolled in this phase I trial between December 2019 and March 2021. Except for one patient who was deemed ineligible because a preoperative echocardiogram revealed an improved LVEF of 52%, six patients underwent randomization in a double-blind manner (ADSC group, n = 3; placebo group, n = 3). All planned surgeries were successfully completed and the patients discharged as scheduled. One patient in the placebo group could not undergo postoperative examinations at 24 weeks because of worsening heart failure symptoms after 12 weeks due to excessive food and fluid intake. However, the remaining five patients underwent scheduled postoperative examinations for up to 24 weeks.

Preoperative characteristics and operative procedures

As shown in Table 1, all patients were men with a median age of 66.5 years and a mean body mass index of 23.5 kg/m^2. All patients had a history of smoking, while four had dyslipidemia, three had hypertension, and one had diabetes as risk factors for coronary artery disease. Three patients exhibited NYHA II heart failure symptoms, while three had NYHA III heart failure symptoms. All patients were receiving preoperative cardioprotective drugs, mainly β-blockers; the same medication was maintained in the postoperative period (Supplemental Table). Regarding CABG (Table 2), five patients underwent on-pump beating CABG, while the remaining patient from the placebo group received off-pump CABG. The left internal thoracic artery was used in all patients and the bilateral internal thoracic arteries in five patients, with a mean 3.5 anastomosis sites. The median operative time was 324 min, while the mean blood loss was 1040 mL. The administration of fibrin glue, including ADSCs or placebo, was uneventful in all patients.

Table 1 Preoperative characteristics

Patient	Group	Age	Sex	BMI	Coronary risk factors	NYHA classification
Case 1	ADSC	60	Male	23	HL, smoking	2
Case 2	ADSC	69	Male	18	HT, HL, smoking	3
Case 3	ADSC	62	Male	24	HT, smoking	2
Case 4	Placebo	74	Male	26	DM, HT, HL, smoking	3
Case 5	Placebo	64	Male	22	HL, smoking	2
Case 6	Placebo	72	Male	24	Smoking	3

ADSC adipose-derived stem cell, *BMI* body mass index, *HL* hyperlipidemia, *HT* hypertension, *DM* diabetes mellitus, *NYHA* New York Heart Association

Table 2 Operative procedure

Patient	Group	CABG procedure	Anastomosis	CPB	OP time (min)	Blood loss (ml)
Case 1	ADSC	LITA-LAD, RITA-RA-4PD-PL	3	+	342	680
Case 2	ADSC	LITA-LAD, RITA-RA-Dx-PL-4PD	4	+	291	1260
Case 3	ADSC	LITA-LAD, RITA-RA-HL-PL-4PD	4	+	337	820
Case 4	Placebo	LITA-LAD, SVG-Dx-PL, SVG-4PD	4	+	322	3740
Case 5	Placebo	LITA-LAD, RITA-RA-D1-PL	3	–	310	2968
Case 6	Placebo	RITA-LAD, LITA-PL	2	+	326	580

CABG coronary artery bypass grafting, *LAD* left anterior descending artery, *4PD* posterior descending artery, *PL* posterolateral artery, *Dx* diagonal branch, *HL* high lateral branch, *LITA* left internal thoracic artery, *RITA* right internal thoracic artery, *RA* radial artery, *SVG* saphenous vein graft, *CPB* cardiopulmonary bypass, *OP* operation

Adverse events

The adverse events that were unequivocally linked to the products used in the trial, including ADSCs, were limited to pleural effusion, which was resolved by drainage in one patient in the ADSC group. Other events indisputably related to the CABG procedure included transient perioperative paroxysmal atrial fibrillation in two ADSC group patients and a wound infection in one placebo group patient, both of which resolved spontaneously (Table 3).

Table 3 Adverse events

Patient	Group	Undeniable association with the products of the trial	Undeniable association with the CABG procedure
Case 1	ADSC		pAf
Case 2	ADSC		pAf
Case 3	ADSC	Pleural effusion	
Case 4	Placebo		Wound infection
Case 5	Placebo		
Case 6	Placebo		

pAf paroxysmal atrial fibrillation

Reduced LGE-MRI volume and improved LV function in ADSC group

A comparison of the changes in LGE-MRI volume before and 24 weeks after surgery revealed a decrease in all three ADSC groups versus no apparent changes in the placebo group (Fig. 1a, b). In terms of left ventricular function, MRI (Fig. 1c–e), CCT (Fig. 2a–c), and echocardiography (Fig. 2d–f) demonstrated decreased left ventricular diastolic and systolic volumes and an increased LVEF over time in the ADSC group. Conversely, in the placebo group, no significant changes in the left ventricular volume or LVEF were observed after surgery (Fig. 2).

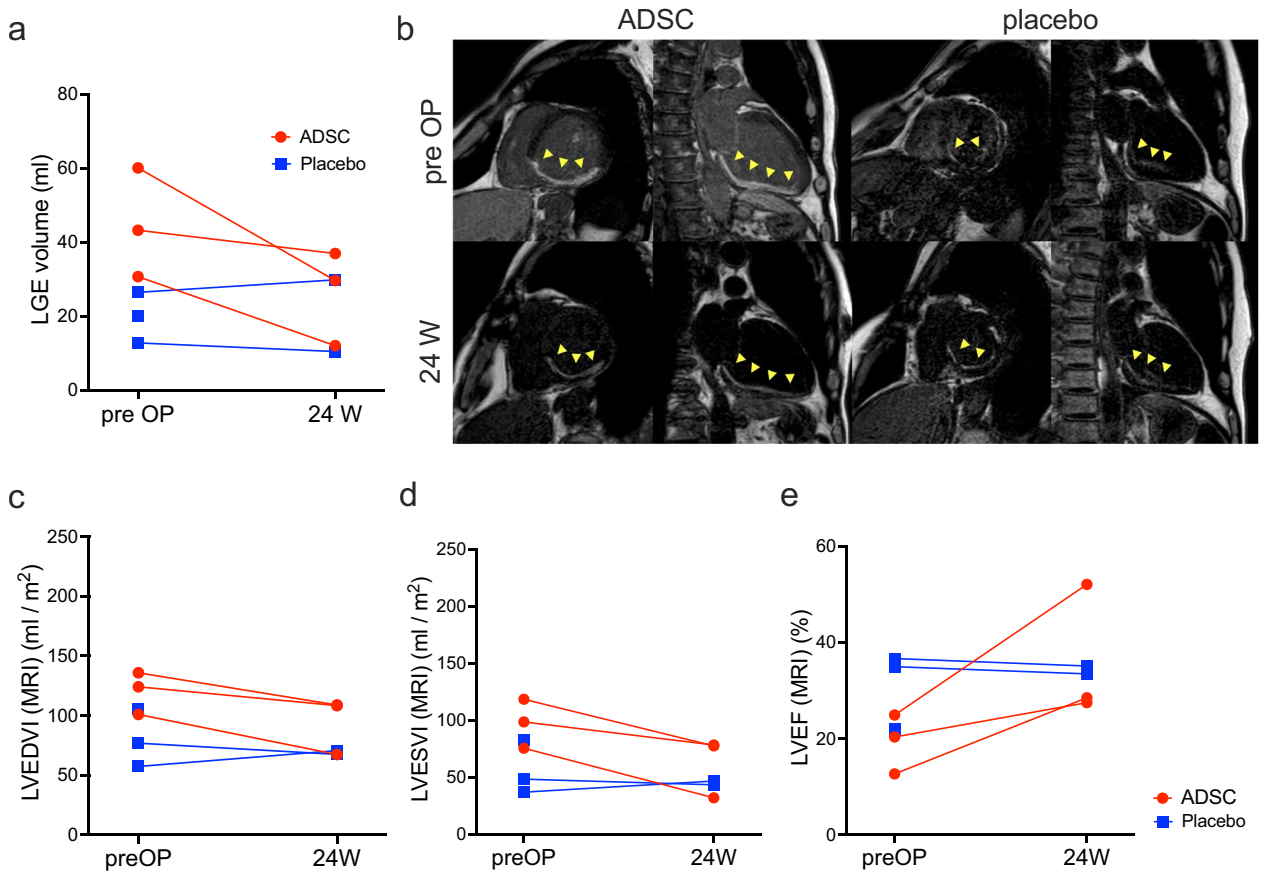


Fig. 1 LGE-MRI and cardiac function before versus after surgery. The LGE-MRI volumes before versus 24 weeks after surgery (**a**). Representative images are shown for patient 3 in the ADSC group and patient 5 in the placebo group (**b**). The yellow triangles indicate the LGE sites. Images of the other patients are shown in Figure S1. Left ventricular end-diastolic volume index (LVEDVI) (**c**) and left ventricular end-systolic volume index (LVESVI) (**d**) were measured simultaneously, and left ventricular ejection fraction (LVEF) (**e**) was calculated

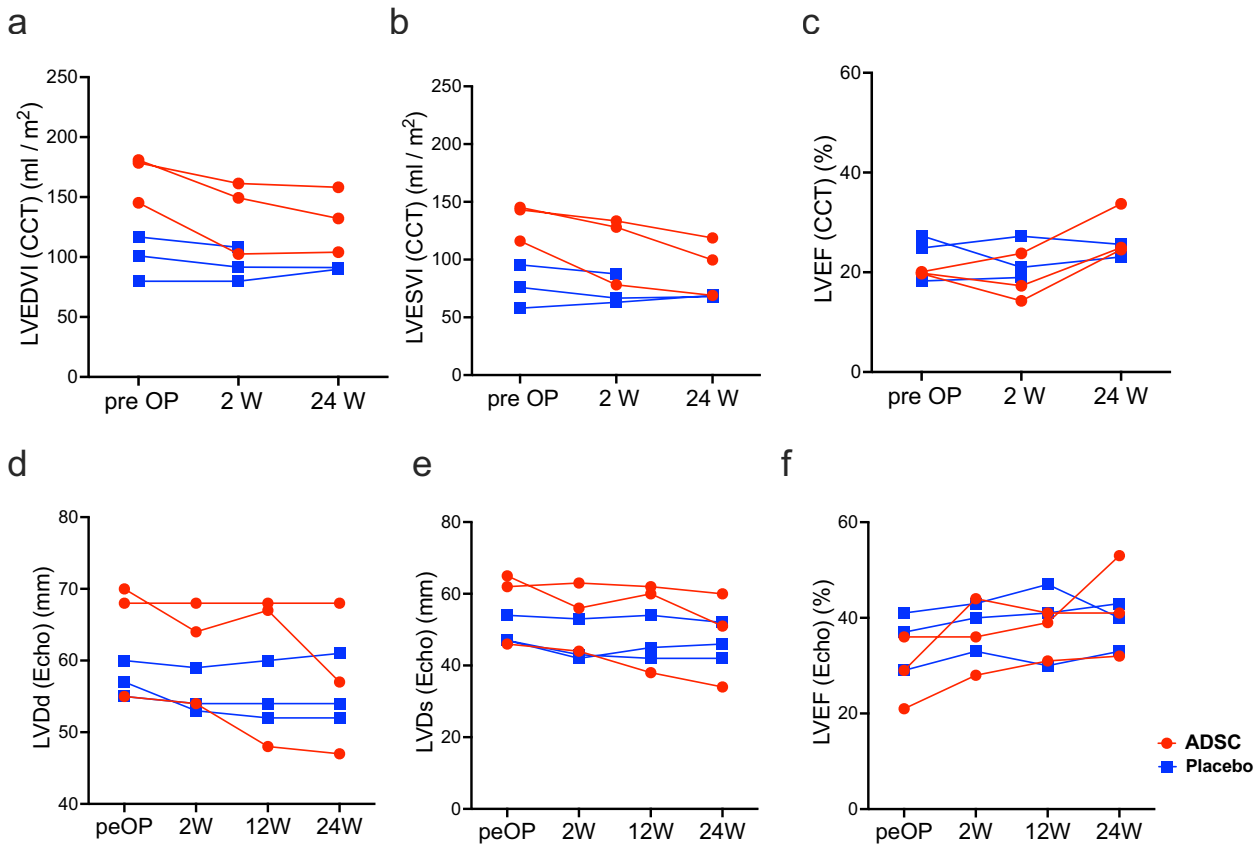


Fig. 2 Cardiac function before versus after surgery. Left ventricular end-diastolic volume index (LVEDVI) (**a**) and left ventricular end-systolic volume index (LVESVI) (**b**) were simultaneously measured using cardiac computed tomography (CCT), and left ventricular ejection fraction (LVEF) (**c**) was calculated. Left ventricular diastolic diameter (LVDd) (**d**), left ventricular systolic diameter (LVDs) (**e**), and LVEF (**f**) were measured on the echocardiography (echo) images

Changes in heart failure status

One patient in the ADSC group exhibited a marked improvement in exercise tolerance as measured by the 6-min walk distance, whereas no significant change was noted after CABG in the other patients (Fig. 3a). In the ADSC group, all patients with preoperative NYHA class II or III heart failure symptoms improved to NYHA class I. In contrast, one patient in the placebo group showed improved heart failure symptoms initially after the procedure that worsened after 12 weeks, eventually reaching NYHA III (Fig. 3b). The MLHFQ scores for all patients were collected, except for one in the ADSC group owing to a procedural error at the 24-week mark. The remaining data are presented in Fig. 3c. Notably, one patient in the ADSC group, who had a high preoperative score of 50 points, showed significant improvement with a much lower score, indicating an enhanced quality of life. In contrast, the similarly high preoperative score of 47 points in the placebo group worsened to 54 points at 24 weeks, suggesting a decreased quality of life. Blood NT-proBNP levels transiently increased after surgery in all patients in both groups except for the one patient in the placebo group whose heart failure symptoms worsened 12 weeks after surgery and returned to nearly preoperative levels at 24 weeks (Fig. 3c).

Discussion

In this investigator-initiated trial, six patients with ischemic cardiomyopathy and an LVEF of ≤40% who were indicated for revascularization by CABG underwent double-blind procedure—three with ADSC spray transplantation and three with placebo—and were observed for 24 weeks. All patients underwent ADSC spray implantation without complications. One case of postoperative pleural effusion in the ADSC group (Table 3) could not be completely ruled out as being related to ADSC transplantation but was resolved by drainage. The LGE-MRI volume decreased in all patients in the ADSC group versus no significant changes were observed in two patients (Fig. 1). In addition, all patients in the ADSC group showed improved left ventricular function, whereas those in the placebo group showed no clear

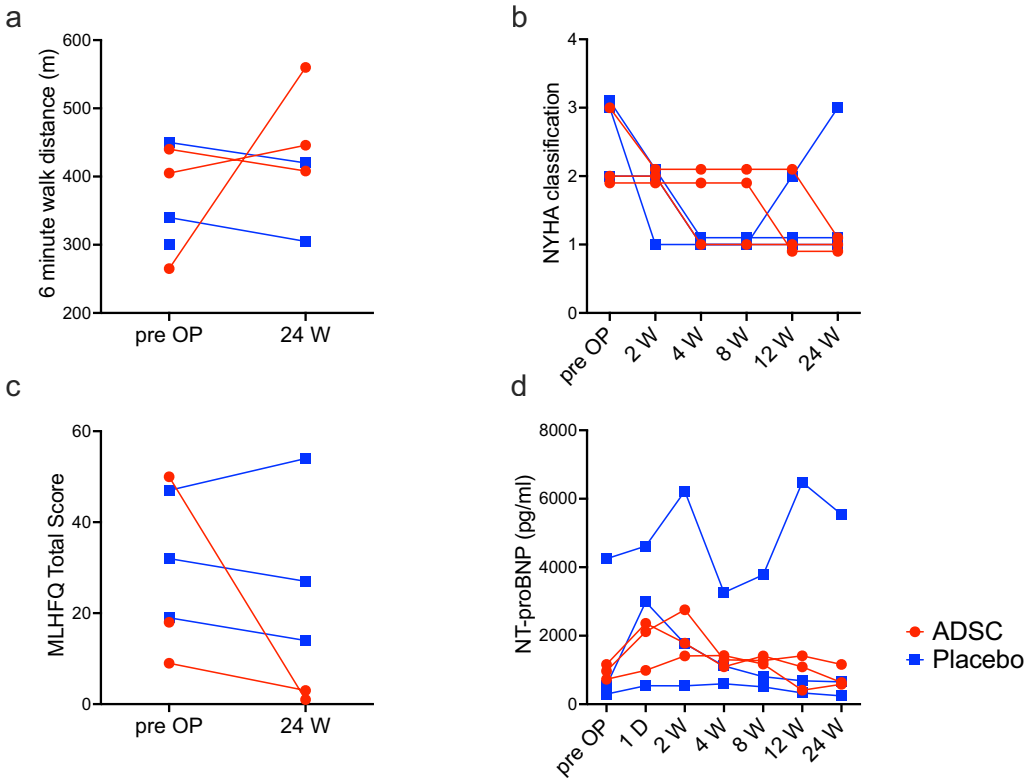


Fig. 3 Serial changes in heart failure status before versus after surgery. Six-minute walk distance (**a**), change in heart failure symptoms according to New York Heart Association (NYHA) classification (**b**), total Minnesota Living with Heart Failure Questionnaire (MLHFQ) score (**c**), and *N*-terminal pro-brain natriuretic peptide (NT-proBNP) levels in the blood (**d**) before versus 24 weeks after surgery

improvement (Figs. 1c–e, 2). One patient in the ADSC group showed markedly improved exercise tolerance in terms of 6-min walk distance (Fig. 3a), while postoperative heart failure symptoms improved to NYHA I in all but one patient in the placebo group, who had worsening heart failure symptoms (Fig. 3b).

CABG is a treatment method for ischemic cardiomyopathy that improves patient prognosis by improving blood flow to the myocardial tissue [4], revitalizing the hibernating myocardium, and improving cardiac function [17]. However, CABG can only revascularize the major coronary arteries, and additional treatment to construct a microvascular network in the myocardial tissue is required to further improve cardiac function. The interstitium of the myocardial tissue may contain hibernating cardiomyocytes in the border region as observed on LGE-MRI, while improving blood flow may decrease the LGE-MRI-determined volume. However, CABG alone does not reduce LGE-MRI volume [13, 14], suggesting that additional interventions may be necessary. In this study, ADSCs transplanted onto the cardiac surface after CABG combined with fibrin glue reduced postoperative LGE-MRI volume and improved cardiac function (Fig. 1). This finding suggests that the paracrine angiogenic effect of ADSCs may add to the revascularizing effect of CABG, increasing blood flow in the myocardial tissue and improving cardiac function by reactivating the hibernating myocardium.

Cell transplantation therapies targeting heart failure reported to date include intramyocardial injections to act on the myocardial tissue [8] or intravenous systemic administration to reduce procedural invasiveness [18, 19]. Intramyocardial injection is associated with problems such as bleeding and arrhythmogenesis [20], whereas systemic intravenous administration is associated with limited cell types that can act on the myocardial tissue. The method employed in this study, in which the cells were mixed with fibrin glue and sprayed onto the surface of the heart for transplantation, has never before been used in the clinical setting. This method can be conducted in the same manner as the fibrin glue spray used in conventional CABG for hemostasis and is considered technically simple and unlikely to cause any problems. Moreover, because we used cryopreserved cells, no special cell culture facilities were required. Therefore, this method is considered highly versatile. Our method involves the release of angiogenic factors from transplanted cells. ADSCs secrete angiogenic factors such as vascular endothelial growth

factor and hepatocyte growth factor in vitro as well as the chemokine stromal cell-derived factor 1, which induces angiogenesis through myeloid cell migration. Human ADSCs transplanted into pig models of ischemic cardiomyopathy persisted for up to 4 weeks post-transplantation and restored cardiac by inducing angiogenesis [12]. This finding suggests that a similar mechanism may have contributed to the restoration of cardiac function observed in our study. In addition, preclinical studies have shown that mitochondria from transplanted cells migrate to the heart and exert therapeutic effects [9]. Both mechanisms are thought to act on the hibernating myocardium, which is expected to recover from ischemic cardiomyopathy and promote functional recovery. Based on findings reported to date [15], our approach may contribute to the improved patient prognosis.

Study limitations

This phase I trial focused on safety and feasibility in a minimal cohort of six patients. The small number of patients limited the analysis of the treatment effect in the ADSC versus placebo groups. In addition, all patients in the current trial were male; therefore, sex-related differences in the impact of ADSC transplantation, including treatment efficacy, could not be examined. This issue should be addressed in the next phase of the trial with a larger number of patients and representation of both sexes.

Conclusions

Cell spray transplantation of ADSCs combined with CABG for ischemic cardiomyopathy may be feasible and safe and could potentially enhance the therapeutic effects of CABG. However, its therapeutic efficacy should be confirmed in future phase II and III clinical trials.

Abbreviations

ADSC	Adipose-derived stem cell
CABG	Coronary artery bypass grafting
CCT	Cardiac computed tomography
Echo	Echocardiography
LGE-MRI	Late gadolinium-enhanced magnetic resonance imaging
LVEF	Left ventricular ejection fraction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MSC	Mesenchymal stem cell
NT-proBNP	*N*-Terminal pro-brain natriuretic peptide
NYHA	New York Heart Association

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-024-05816-1.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Acknowledgements

This investigator-initiated clinical trial was supported by Rohto Pharmaceutical Co., Ltd., which we thank for its assistance with this study.

Author contributions

T.K., D.Y., A.K., Y.M., S.S., T.Y., H.H., and S.M. conducted the surgeries. D.M. and S.M. designed the clinical trial. D.M. provided the technical support for this study. T.K. wrote the paper.

Funding

This clinical trial was supported by the Japan Agency for Medical Research and Development (Grant Numbers JP23bk0304002 and JP24bk0304005).

Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This clinical trial was approved by the Ethical Review Committee of Osaka University (Approval No. 199006). Written informed consent was obtained from all participants.

Consent for publication

Written informed consent for the publication of individual data was obtained from all patients.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, 2-2 Yamada-Oka, Suita, Osaka 565-0871, Japan.

Received: 28 June 2024 Accepted: 29 October 2024
Published online: 02 December 2024

References

1. Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium." J Am Coll Cardiol. 1986;8:1467–70.
2. Kloner RA. Stunned and hibernating myocardium: where are we nearly 4 decades later? J Am Heart Assoc. 2020;9: e015502.
3. Ryan MJ, Perera D. Identifying and managing hibernating myocardium: what's new and what remains unknown? Curr Heart Fail Rep. 2018;15:214–23.
4. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med. 2016;374:1511–20.
5. Nakae M, Kainuma S, Toda K, Miyagawa S, Yoshikawa Y, Hata H, Yoshioka D, Kawamura T, Kawamura A, Kashiyama N, et al. Incidence, determinants and clinical impact of left ventricular function recovery after surgical treatments for ischaemic cardiomyopathy. Eur J Cardiothorac Surg. 2021;60:689–96.
6. Braunwald E. The war against heart failure: the Lancet lecture. Lancet. 2015;385:812–24.
7. Si Z, Wang X, Sun C, Kang Y, Xu J, Wang X, Hui Y. Adipose-derived stem cells: sources, potency, and implications for regenerative therapies. Biomed Pharmacother. 2019;114: 108765.
8. Qayyum AA, van Klarenbosch B, Frljak S, Cerar A, Poglajen G, Traxler-Weidenauer D, Nadrowski P, Paitazoglou C, Vrtovec B, Bergmann MW, et al. Effect of allogeneic adipose tissue-derived mesenchymal stromal cell treatment in chronic ischaemic heart failure with reduced ejection fraction—the SCIENCE trial. Eur J Heart Fail. 2023;25:576–87.
9. Mori D, Miyagawa S, Kawamura T, Yoshioka D, Hata H, Ueno T, Toda K, Kuratani T, Oota M, Kawai K, et al. Mitochondrial transfer induced by adipose-derived mesenchymal stem cell transplantation improves

cardiac function in rat models of ischemic cardiomyopathy. Cell Transplant. 2023;32:9636897221148456.
10. Mori D, Miyagawa S, Kido T, Hata H, Ueno T, Toda K, Kuratani T, Oota M, Kawai K, Kurata H, et al. Adipose-derived mesenchymal stem cells preserve cardiac function via ANT-1 in dilated cardiomyopathy hamster model. Regen Ther. 2021;18:182–90.
11. Mori D, Miyagawa S, Matsuura R, Sougawa N, Fukushima S, Ueno T, Toda K, Kuratani T, Tomita K, Maeda N, et al. Pioglitazone strengthen therapeutic effect of adipose-derived regenerative cells against ischemic cardiomyopathy through enhanced expression of adiponectin and modulation of macrophage phenotype. Cardiovasc Diabetol. 2019;18:39.
12. Mori D, Miyagawa S, Yajima S, Saito S, Fukushima S, Ueno T, Toda K, Kawai K, Kurata H, Nishida H, et al. Cell spray transplantation of adipose-derived mesenchymal stem cell recovers ischemic cardiomyopathy in a porcine model. Transplantation. 2018;102:2012–24.
13. Steinhoff G, Nesteruk J, Wolfien M, Kundt G, Börgermann J, David R, Garbade J, Große J, Haverich A, Hennig H, et al. Cardiac function improvement and bone marrow response: outcome analysis of the randomized PERFECT phase III clinical trial of intramyocardial CD133(+) application after myocardial infarction. EBioMedicine. 2017;22:208–24.
14. Pätilä T, Lehtinen M, Vento A, Schildt J, Sinisalo J, Laine M, Hämmäinen P, Nihtinen A, Alitalo R, Nikkinen P, et al. Autologous bone marrow mononuclear cell transplantation in ischemic heart failure: a prospective, controlled, randomized, double-blind study of cell transplantation combined with coronary bypass. J Heart Lung Transplant. 2014;33:567–74.
15. Kancharla K, Weissman G, Elagha AA, Kancherla K, Samineni S, Hill PC, Boyce S, Fuisz AR. Scar quantification by cardiovascular magnetic resonance as an independent predictor of long-term survival in patients with ischemic heart failure treated by coronary artery bypass graft surgery. J Cardiovasc Magn Reson. 2016;18:45.
16. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop D, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8:315–7.
17. Perry AS, Mann DL, Brown DL. Improvement of ejection fraction and mortality in ischaemic heart failure. Heart. 2021;107:326–31.
18. Ghiroldi A, Piccoli M, Cirillo F, Monasky MM, Ciconte G, Pappone C, Anastasia L. Cell-based therapies for cardiac regeneration: a comprehensive review of past and ongoing strategies. Int J Mol Sci. 2018;19:3194.
19. Braunwald E. Cell-based therapy in cardiac regeneration: an overview. Circ Res. 2018;123:132–7.
20. Menasché P, Alfieri O, Janssens S, McKenna W, Reichenspurner H, Trinquart L, Vilquin JT, Marolleau JP, Seymour B, Larghero J, et al. The myoblast autologous grafting in ischemic cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. Circulation. 2008;117:1189–200.

Publisher's Note