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Case Report

Our Experience with Stem Cell Applications in Patients with Advanced Peripheral Arterial Disease

Sefer Usta*

Trabzon Ahi Evren Cardiac and Thoracic Surgery Unit, Cardiovascular SUAM, University of Health Sciences, Trabzon, Turkey

Abstract

Objective: To assess the results of stem cell applications in patients with peripheral arterial disease who could not undergo surgical treatment due to advanced-stage ischemia.

Study design: Patients who could not undergo revascularization due to distal vascular insufficiency were recruited into this study between June 2009 and 2015. Stem cells obtained via bone marrow aspiration were utilized in 30 patients (17 male, 13 female; mean age, 56.2 y), and stem cells obtained from abdominal fat tissue were utilized in another 30 patients (22 male, 8 female; mean age, 58.9 y). Twenty patients with similar clinical symptoms who received medical treatment only comprised the control group for comparisons.

Results: Stem cells were harvested from the bone marrow under local anesthesia, while general anesthesia was used for collecting stem cells of adipose tissue origin. Cells collected from each patient were processed in mobile units and were ready to use within approximately 1 hour. The harvested stem cells were administered percutaneously via intramuscular injections into the target tissues, conforming to vascular anatomy. Clinical status, ankle-brachial indices, pulse oximetry, and walking distance with exercise test were assessed at 1, 3, and 6 months after the procedures.

Conclusion: Stem cell applications performed in patients unfeasible for revascularization appear to be associated with improvements in clinical symptoms, quality of life, and walking distance. We believe that this therapy may help reduce the rate of amputation

More Information

***Address for correspondence:** Sefer Usta, Trabzon Ahi Evren Cardiac and Thoracic Surgery Unit, Cardiovascular SUAM, University of Health Sciences, Trabzon, Turkey, Email: seferusta2000@yahoo.com

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Critical leg ischemia remains associated with high morbidity and mortality, and is defined by the presence of ischemic symptoms during rest, as opposed to symptoms occurring during physical exertion in intermittent claudication. Patients with critical leg ischemia may have trophic skin changes, ulcers, and gangrene. Unless successful revascularization is performed, major amputations are unavoidable. Also, these patients experience an increased occurrence of cardiovascular events. In developed countries, each year, 500 to 1000 patients per 100.000 population are newly diagnosed, and this figure rises with age and the presence of diabetes [1].

Stem cells are defined as undifferentiated embryonic cells with the potential to divide and regenerate, which is retained following birth to replace dead or dysfunctional specific tissue cells. In patients with severe critical ischemia, the blood circulation in the ischemic extremity should be directly and rapidly restored in order to obtain symptomatic improvement and limb salvage. Several surgical, stenting/balloon, and atherectomy catheters have been utilized for that purpose. As a result of advances in both open and minimally invasive surgical techniques, many patients with severe chronic peripheral arterial disease may benefit from these procedures that can directly increase the blood flow to the extremity. As a result of more widespread use of these medical and surgical interventions, a 21% reduction has been reported in amputations. Despite such advances, major amputations (amputations above the ankle) are not uncommon. Approximately 20% of the patients with no or inadequate treatment die, and 50% to 90% require below-knee or above-knee amputations within 6 months [2]. Currently, there is an urgent unmet need for better or alternative revascularization techniques to achieve further reduction in amputations, and to negate the significant negative impact of amputations on life quality and expectancy.

A peripheral arterial pressure that is consistently below 60 mmHg may be associated with the spontaneous development of necrosis and ulcerations. In these patients, minor wounds cannot heal, subsequently progressing into necrosis and ulcers. Thus, we explored the role of stem cell transplantation in the regeneration of ischemic tissues in patients with peripheral arterial disease.

Patients and methods

Stem cell transplantation was performed in a total of 60 patients between June 2009 and June 2015 at the Surgery Unit of AhiEvren Cardiovascular Surgery Hospital (51 male, 9 female; mean age 50.4 years, range: 25-65 years). Of these, 30 received regenerative stem cells of bone marrow origin and 30 stem cells of adipose tissue origin. The source of stem cells was selected on a random basis, with special care to allow for similar demographic characteristics across the two groups. Also, 20 patients with similar clinical symptoms served as controls and received medical treatment consisting of cilostazol + acetyl salicylic acid. In all patients, the ankle-brachial index was < 0.8.

The following criteria were used for patient selection:

1. Absolute occlusion pressure of < 70 mmHg at the ankle or ABI < 0.8
2. Occlusive pressure of < 60 mmHg at the great toe or a TBI < 0.6
3. Age > 18 y and ability to comprehend the planned treatment.
4. Lack of shortened life expectancy of < 6 months due to comorbid conditions
5. Absence of a history of bone marrow disease (particularly NHL, MDS) that precludes transplantation
6. Absence of life-threatening complications of ischemia requiring urgent amputation
7. Absence of pregnancy or breastfeeding.
8. No history of major cardiovascular procedures or events within the past 30 days

Six patients in the study groups with active infection and elevated CRP levels underwent the procedures after appropriate antibiotherapy and normalization of CRP. Nine patients had a diagnosis of Buerger's disease, and 51 with ischemic peripheral arterial disease. Eight patients had critical ischemia that would soon require amputation. The procedure was bilateral in 3 patients and unilateral in 57. In all patients attending the outpatient or emergency unit, a tomographic peripheral angiography was performed before the procedure to evaluate the distal vessel bed and to confirm the below-knee vascular insufficiency. Except for patients with active wounds and tissue necrosis, a treadmill test at 3.5 km/h with a slope of 10% was administered to measure maximum walking distance and pain-free walking distance. All patients received low molecular weight heparin and trental (450 mg/day) in Rheomacrodex. Six patients with infections received antibiotic treatment based on the susceptibility test results until normalization of CRP. All procedures were carried out in the operating room, with local anesthesia under sedation for the hematopoietic stem cell group or under mild general anesthesia with a mask.

Anesthesia procedure

The patients were routinely monitored by Electrocardiography (ECG), peripheral oxygen saturation (SpO_2), and noninvasive blood pressure, and the values were recorded. After intravenous peripheral venous cannulation with an 18-gauge, appropriate infusion of crystalloid solution was started. All patients were administered 2 L/min O_2 by nasal cannula. After monitoring, patients were administered intravenous fentanyl 1 µ/kg and midazolam 0.05 mg/kg. If sufficient patient comfort cannot be provided to Group 1, midazolam (1-3 mg iv bolus), propofol infusion (propofol fresenius vial; 2-5 mg/kg/hour), ketamine (1 mg/kg iv bolus; ketalar) during the procedure when deemed necessary by the anesthetist vial, pfizer) The agent was applied. In addition to group 2, 50% O_2 + 50% NO_2 + sevoflurane (Sevorane, Abbott) inhalation was performed with a mask to maintain anesthesia. At the end of the surgery, the patients were taken to the postoperative room and followed up. Patients with an Aldrete score > 9 were sent to the service. For the mesenchymal stem cell group.

For hematopoietic procedures, 240 ml of blood was collected from the anterior iliac spine, and 60 ml of aspirate was obtained following centrifugation in special sterile incubators (sterile Falcon tubes). For mesenchymal procedures, a 1 cm incision was made below the umbilicus, and 80 ml of adipose tissue was aspirated via liposuction.

The aspirated material was prepared in a centrifugation device and a shaking incubator to achieve 20 ml of aspirate. Stem cells within the processed aspirates (mainly CD34 + and AC133 + for hematopoietic procedures, and CD34-, CD45-, and CD14- for mesenchymal procedures) were administered locally without anesthesia to the anterior and posterior compartments below the knee, conforming to vascular anatomy. In hematopoietic procedures, one-third of the preparation (i.e., 20 ml) was administered percutaneously

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via the femoral artery into the treated extremity. Patients were discharged the next day with appropriate medical prescriptions and advice. Also, all patients were instructed to walk for at least 30 minutes per day. Smoking was discouraged in all smokers, with confirmation of abstinence from smoking at follow-up visits (Figures 1-3).

Ankle-brachial index, pulse oximetry, and walking distance were assessed at postoperative 1, 3, and 6 months. At 6 months, a follow-up peripheral tomographic angiography was performed. Graph 1, Table 1 shows the results of preoperative and postoperative assessments in 60 patients undergoing stem cell transplantation.

Results

Elastic bandages were applied to all patients, who were discharged one day after the procedure. Depending on the clinical condition of the patient, treatment with Low Molecular Weight Heparin (LMWH) + cilostazol or cilostazol + acetyl salicylic acid treatments were given. In patients with severe ischemia receiving LMWH, a switch to standard treatment with cilostazol + acetyl salicylic acid was made after 1 month. This standard treatment was continued for 6 months in all patients. At follow-up visits (1, 3, and 6 months), ankle brachial index, pulse oximetry, and treadmill walking distance were evaluated. Also, clinical history was obtained, and physical examination was performed (Tables 2,3, Figures 4,5).

Following intra-arterial + intramuscular stem cell transplantation, a significant increase in ABI was noted, together with significant growth in pain-free maximum walking distance and mild improvement in skin saturation index. In those with extremity wounds, the wound healing process also appeared to be accelerated. Tomographic angiography at 6 months showed the formation of small new vessels as a result of angiogenesis in one-third of the patients. Of the 8 patients with critical ischemia that could require amputation, major amputation was performed in 2, and minor amputation in 1. The two patients who required major amputation were those who had undergone therapy with stem cells of adipose origin. A patient with a minor amputation had received stem cells of bone marrow origin.

Statistical Analysis: Data are given as mean ± standard deviation for those with normal distribution, and as median (gap of quarters) for those without normal distribution. Categorical variables were expressed as numbers and percentages. SPSS 24 (Statistical Package for Social Sciences software, SPSS Inc., Chicago, Illinois, USA) program was used in the analysis of the research. In group comparisons, the chi-square test was used if frequency was compared for categorical variables, the independent sample t - test was used if mean values were compared in continuous variables,

Figure 1: Bone marrow aspiration.

Figure 2: Abdominal aspiration of adipose tissue and administration at the extremity.

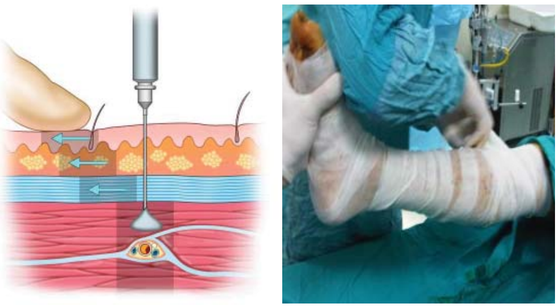


Figure 3: The route of administration, followed by appropriate dressing.

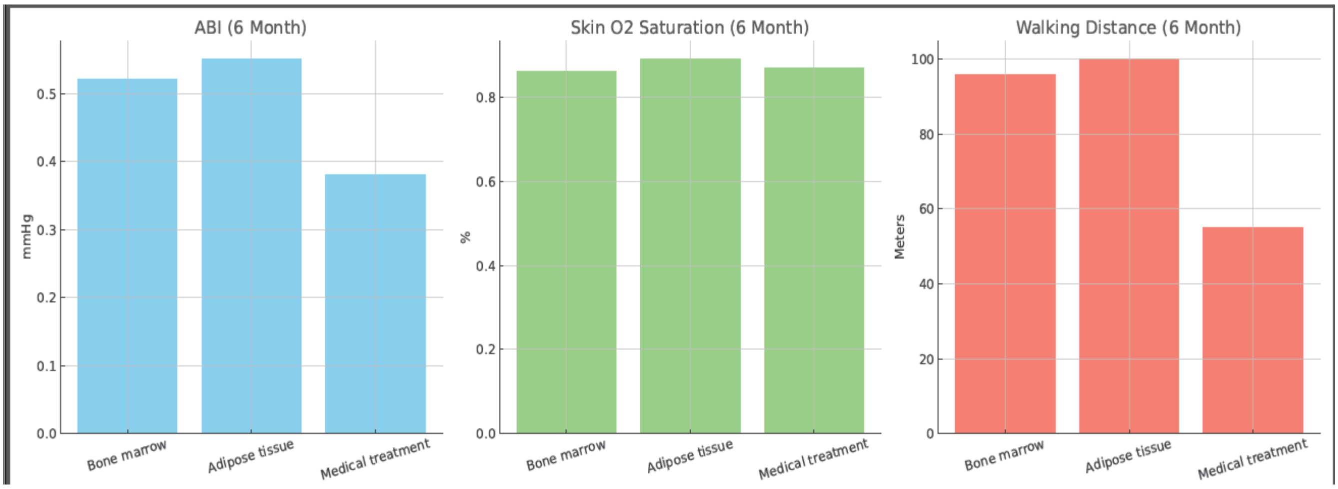
Figure 4: Exemplary CT angiographic images preoperatively and at postoperative month 6.

Figure 5: Exemplary CT angiographic images preoperatively and at postoperative month 6.

Table 1: Preoperative and postoperative assessments in patients receiving stem cell therapy.

Group	Ankle-brachial index (mmHg)					Skin O2 saturation (%)				Walking distance (m)			
	Preoperative		Postoperative			Preoperative	Postoperative			Preoperative	Postoperative		
	Before exercise	After exercise	1 mth	3 mth	6 mth		1 mth	3 mth	6 mth		1 mth	3 mth	6 mth
I.Bone marrow (mean)	0.31	0.26	0.45	0.52	0.60	0.84	85	86	88	44	60	96	125
II.Adipose tissue (mean)	0.30	0.25	0.54	0.55	0.1	86	88	88	89	47	61	100	124
III.Medical treatment (mean)	0.33	0.30	0.36	0.38	0.41	88	87	88	87	48	51	55	55

Statistical Analysis, Group I and II: $p < 0.05$; Group III: $p > 0.05$.



Graph 1

Table 2: Demographic characteristics of the patients.

	Number			Percentage	Mean ± SD	Controls
Age		Bone Marrow	Fat		50.4±6.91	54.2±3.16
Gender Male Female	 51 9	 25 4	 26 5	 85 15		 16 (%80) 4 (%20)
Coronary artery disease	9	4	5	15		6 (%30)
Diabetes	16	10	6	26.6		9 (%45)
Hyperlipidemia	21	8	13	35		9 (%45)
Hypertension	14	6	8	23.3		7 (%35)
COPD	3	1	2	5		4 (%20)
Buerger's disease	9	4	5	15		3 (%15)
Amputation margin	8	5	3	13.3		0
Smoking	54	20	34	90		17 (%85)
Rutherford category Category 4 Category 5 Category 6	 16 30 14	 8 17 6	 8 13 9	 26.6 50 23.4		 5 (%25) 10 (%50) 5 (%25)

COPD: Chronic Obstructive Pulmonary Disease

Table 3: Assessment of the Lower Extremity Ischemia.

Clinical signs	ABI	Toe pressure	Treadmill test (TT)/PVR
Asymptomatic	≥ 1.0	% 80 of the brachial pressure	Normal TT
Mild claudication	> 0.8	> 60 mm Hg	TT completed, post-exercise AP< 50 mmHg
Mild-to-moderate claudication	0.4-0.8	> 40 mm Hg	Unable to complete TT, post-exercise AP< 50 mmHg
Ischemic resting pain	< 0.4	< 30 mm Hg	Metatarsal PVR flat or minimally pulsatile
Tissue loss	< 0.5	< 40 mm Hg	Ankle PVR flat, rarely pulsatile
Limb threat	< 0.15		No arterial signal is detected on Doppler; however, a signal can be detected at the ankle, with mild sensory or motor loss.
Irreversible ischemia	0.0		Arterial signal absent even at ankle level, limb anesthesia, and paralysis

PVR: Pulse Volume Recording

and Mann Mann-Whitney non-parametric test was used if median values were compared. The limit of significance in the analyses was accepted as $p < 0.05$.

Discussion

In the past 10-year period, it has become evident that tissues harbor their stem cells, despite having limited differentiation potential, and these stem cells may be utilized for clinical applications. Many recent studies also indicate the presence of cells with the potential to differentiate into multiple cell types in adult tissues. The regenerative or therapeutic role of stem cells has attracted particular attention, especially when one considers the ample evidence showing the ability of adult stem cells to differentiate into different tissues and cells under the effect of suitable conditions and stimuli [3].

Transplantation of bone marrow stem cells is thought to increase the regenerative potential of the body by improving the tissue functions in areas of ischemia, as well as by augmenting the mobilization of progenitor CD34 + and CD133 + stem cells in the peripheral blood. Previous research suggests that angiogenic treatments may be a plausible option for patients unfeasible for surgical and endovascular procedures [1-3]. Several pilot studies also showed that improved blood flow after stem cell treatment may be effective in improving wound healing, and reducing pain as well as amputations in patients with critical leg ischemia.4 Aspirates of adipose tissue and bone marrow represent a natural source for paracrine, chemokine, and pro-angiogenic cytokines [4,5]. Expansion in vessel diameter represents the single most important physiological repair mechanism in peripheral arterial disease [6].

Measurement of oxygen levels that can diffuse into skin may be useful in assessing the healing potential of ulcers, determining the level of amputation, and evaluating tissue vitality. Patients walk at a speed of 2 m/h with 12% slope increments. This is particularly useful in confirming the vascular etiology of the condition in patients with atypical claudication, and also in determining the severity of intermittent claudication. This test allows identification of the patients with classical symptoms who have relatively normal ABI. Patients are asked to walk for 5 minutes or until no walking is possible due to symptoms. The localization and character of the symptoms, post-exercise decline in AP, and time to return to normal baseline values are important diagnostic parameters. An AP below 50 mmHg after exercise is a defining feature of vascular claudication. A return time to baseline exceeding 5 minutes suggests multiple-level disease with poor collaterals. ABI ranges between 0.5 and 0.9 in patients with vascular claudication, while it is < 0.5 in those with ischemic rest pain and leg ulcers. An Ankle Pressure (AP) of < 40 mmHg indicates critical limb ischemia, with little or no chance of healing when accompanied by tissue loss.

According to the results of our study, medical treatment was associated with a 10% increase in ABI and only a few meters of improvement in walking distance. On the other hand, additional stem cell treatment was associated with a 20% increase in ABI and > 100% increase in walking distance, together with a significant increase in leg skin temperature as well as in daily activities.

Extremity amputations due to peripheral arterial disease represent an important health problem, with major impacts on general well-being and quality of life. Despite recent advances in surgical and endovascular procedures, amputations remain a major health issue. Also, 25% to 40% of patients with this condition receive no benefit from the treatments [7-9]. Expansion of the caliber of the extremity vessels represents the most important physiological repair mechanism in these patients [10]. In our view, stem cell therapy may offer effective limb salvage when endovascular and/or surgical techniques fail to succeed, particularly in patients with severely advanced disease in the distal vessel bed and in those with Buerger's disease. It may also be plausible to perform stem cell therapy in conjunction with surgery in surgical candidates, who are expected to experience graft or stent failure due to weak distal vasculature. However, further studies with a larger sample size are warranted to better elucidate the role of stem cell therapy in this setting.

Conclusion

As a result, we can achieve good results in advanced arterial vascular diseases with stem cell applications, which are increasingly used in almost every field of medicine. With increased stem cell applications and experiences, we can say that we have made significant progress in leg amputation rates, wound healing, and walking distances, thanks to stem cell applications added to the treatment.

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