Stem Cell Therapy in Myocardial Infarction: Still Therapeutic Hope?

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Abstract
Myocardial infarction is still a therapeutic rollercoaster challenge because, despite revolutionary treatments in its management, heart failure is still a consequence. Stem cell therapy might be a turning point in treating myocardial infarction patients for regaining what is lost—that is, myocardial tissue. This paper reviews the latest evidence for using stem cell therapy in the treatment of myocardial infarction, the results of this possible therapy regarding regaining cardiomyocytes, and the extent to which therapy with stem cells can be used in the future for the management of acute coronary syndromes.

Keywords
myocardial infarction, stem cell, therapy, transplant, regenerative medicine.

Rezumat
În zilele noastre, infarctul miocardic reprezintă încă o provocare terapeutică deoarece în ciuda tratamentelor revoluționare în managementul său, insuficiența cardiacă, ca și consecință a acestuia, este supusă unei incidențe crescute. Terapia cu celule stem ar putea fi un punct de cotitură în tratarea pacienților cu infarct miocardic pentru a recupera ceea ce s-a pierdut, adică țesutul miocardic. Aceast review narativ își propune să evidențieze cele mai recente dovezi privind utilizarea terapiei cu celule stem în tratarea infarctului miocardic, rezultatele acestei posibile terapii privind recâștigarea cardiomiocitelor și măsura în care terapia cu celule stem poate fi utilizată în viitor pentru gestionarea sindroamelor coronariene acute.

Cuvinte cheie
infarct miocardic, celule stem, transplant, medicină regenerativă

Introduction

Regenerative medicine has gained ground during past years due to new knowledge concerning stem cells' ability to regenerate tissues, techniques in obtaining this type of cell, and means to induce them to target the troubled tissue. Treatment using stem cells has been used for some time, especially in bone marrow and blood disorders due to the abundance of regenerative cells in these tissues. Nowadays other illnesses are under consideration to be treated with stem-cell transplants, among them being myocardial infarction.

Stem cells: what are they?

Stem cells are immature cells with the capacity to engender new cells in the process called differentiation. There are five main types of stem cells, types based on the extent of their ability to differentiate:

1. totipotent cells (the only cells of this kind are the zygote and blastomere because they give rise to a new individual, being the base for the development of other cells);
2. pluripotent cells (they have a more specific differentiating process than that of the totipotent cells yet they are masters of cell differentiation because they can engender all the kinds of cells that constitute a human body, for example, a blastocyst);
3. multipotent cells (they differentiate into a specific range of cells giving rise to a number of tissue types);
4. oligopotent cells (the differentiation process is narrow, these cells being able to produce few related types; hematopoietic stem cells are the exponent for this group); and,
5. unipotent cells (they have the most limited differentiation process because they can only turn into themselves) [1]. Based on their origin, stem cells are classified into five categories: embryonic, fetal, infant, adult, and induced stem cells (**Table 1, Figure 1**) [2].

Embryonic stem cells are totipotent and pluripotent. Due to being fully differentiated and capable of producing a large range of cells, they are the ideal for stem cell cultivation, yet because of how they are obtained (from embryos that are either produced in the laboratory for study purposes or are left over from fertilization processes or resulting from abortion), which makes them the subject to ethical issues, and because their malignant transformation, they are the least used [1,3].

Stem cells of fetal origin are multipotent, a property that makes them more potent than stem cells of adult origin. Also, they do not exhibit malignant proliferation (as embryonic stem cells do) and have a lower immunogenic effect than adult stem cells, which makes them more suitable for allotransplantation. This group includes cells from the neural crest, and hematopoietic and mesenchymal stem cells. They can be obtained from fetal blood or other fetal tissues such as

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Table 1 - Types of stem cells and their advantages and disadvantages

CELL TYPE	ORIGIN	ADVANTAGES	DISADVANTAGES
EMBRYONIC	Zygote.	Higher differentiation potency. Less risk of cell injury during cultivation due to decreased cell-to-cell adhesion.	Subject to ethical issues due to methods of obtaining them. Malignant transformation (teratoma).
FETAL	Blastocyst. Fetal structures. Bone marrow. Fetal blood.	High differentiation potency. Less risk due to decreased cell-to-cell adhesion in early fetuses. Lower immunogenic effect. Can be obtained from fetal blood.	Subject to ethical issues due to methods of obtaining them.
PERINATAL	Umbilical cord. Placenta. Amniotic fluid.	Multipotent. Can be easily obtained without ethical issues. Lower immunogenic effect.	Differentiation potency is lower than that of fetal cells.
ADULT	Bone marrow. Other structures (liver, kidney).	Oligopotent. No ethical issues. More studies have been based on them; they are already in use for certain disorders.	Differentiation potency is the lowest. Higher immunogenic effect (except for mesenchymal stem cells which express lower amounts of antigens). Obtaining these cells can be painful.
INDUCED PLURIPOTENT	Adult somatic cells genetically modified to resemble embryonic stem cells.	Obtained from adult and perinatal cells (not an ethical issue). High differentiation potency due to the similarity to embryonic cells.	Immunogenic effect.

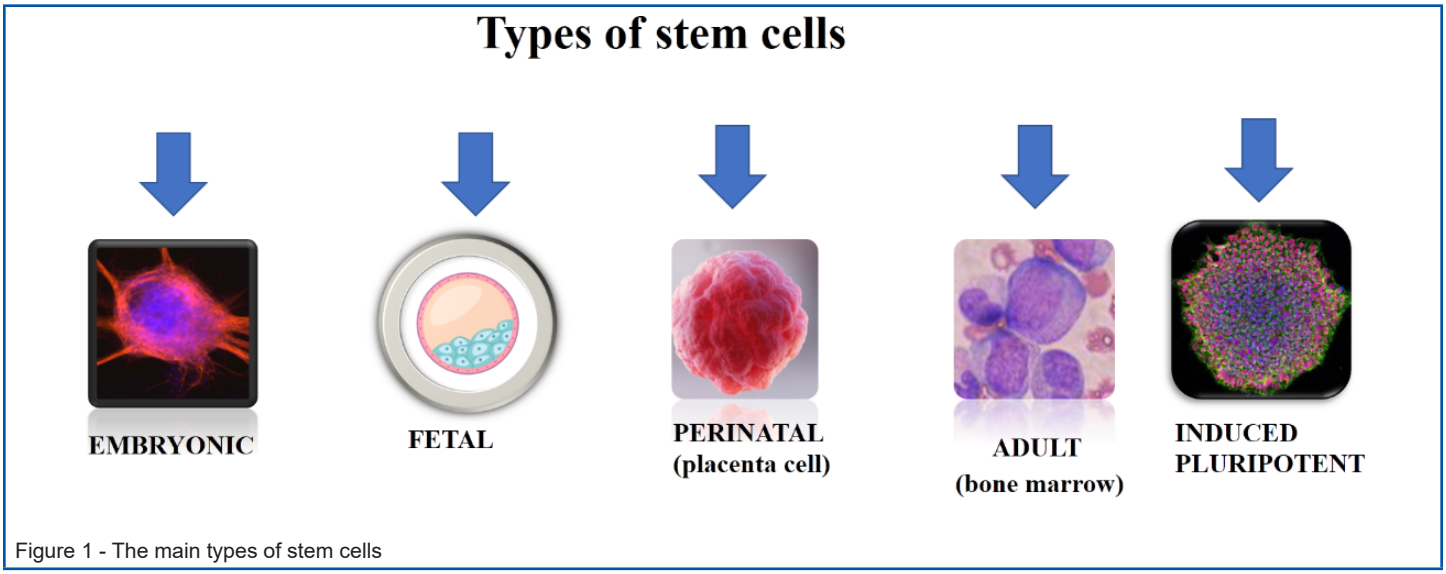


Figure 1 - The main types of stem cells

liver and bone marrow. Due to the fact that fetal blood is a source of stem cells, cultivating stem cells of fetal origin is not strongly subjected to ethical issues [2,4].

Infant stem cells, also called perinatal cells, are obtained from extraembryonic structures at the time of birth (amniotic fluid, placenta, umbilical cord) and have the advantage of being multipotent due to the fact that most of them are mesenchymal stem cells, less immunogenic than those of adult origin. They do not pose ethical issues [5].

Stem cells obtained from adult structures are either oligopotent (out of which the hematopoietic stem cells and mesenchymal stem cells have the highest value) or unipotent. Mesenchymal stem cells, unlike the hematopoietic ones, have a lower immunogenic effect as they lack antigens (HLA type). The major issue of adult stem cells is that their differentiating process is narrower than those of previous cells and obtaining them is part of a painful process. Also, the number of cells that can be obtained is usually smaller and may not be enough for therapy of an individual subject to the need for stem cell therapy [2,6,7].

Induced pluripotent stem cells are obtained in the laboratory from adult or infant cells that are directed to improve their differentiation potency by genetic modification to become similar to embryonic stem cells. Thus, these are embryonic-like cells with the advantage of not raising ethical issues. Their disadvantage is that they retain the high immunogenic effect of adult cells [8,9].

Stem cells in myocardial infarction: the roots of the idea

For many years it was thought that cardiomyocytes have no capacity to renew themselves because they are postmitotic cells that

are no longer capable of mitosis. Recent studies have demonstrated that, in fact, in mammals, thus in humans, the embryonic, fetal, and early newborn heart (for a few days after birth) has the ability to regenerate cardiomyocytes. This property is lost soon after birth, this being the substrate of the heart's inability to repair after myocardial infarction, and instead of healing with restitutio ad integrum, a scar is the final point of the healing process [10].

The idea that stem cells can be used to renew cardiomyocytes lies in the fact that the heart and other body structures comprise progenitor and cardiac stem cells. In the last decades of the last century, it was believed that there were adult stem cells capable of generating cardiomyocytes and that these cells would exist both in the heart and in extracardiac structures, but it was not until the early 2000s that evidence was provided for this. In 2004, Messina et al. have isolated a population of cells called cardiospheres capable of engendering cardiomyocytes [11]. These cardiospheres are a cluster of cells situated in the core which exhibit c-kit receptors (whose ligand is the stem cell factor) and peripheral cells that express other markers of cardiac and stem cells [11]. Up-to-date studies support the aforementioned hypothesis that cardiac cells can regenerate. Mollova and col-laborators have outlined the mathematics of the hypothesis by counting the number of cardiomyocytes; they have determined that the number of cells increases in the first two decades of life (1.1 ± 0.1 × 109 cells in newborn heart versus 3.7 ± 0.3 × 109 in 20-year-old hearts) [12]. Carbon dating was used to measure the turnover of cardiomyocytes and it led to the conclusion that the turnover rate decreases with age, being the highest (yet small) in the first two decades of life (1% per year) and only 0.3% in subjects 75 years of age. Yet this conclusion strengthens the idea of the heart's regenerative capacity [13].

We reviewed the latest five years of trials conducted on stem cell therapies in myocardial infarction provided in full text by PubMed in order to look for further perspectives in myocardial infarction management.

Plenty of ideas, scarcity of reality

Despite the fact that stem cells comprise a variety, their use in myocardial infarction is limited to a few types, most trials focusing on using autologous stem cells rather than allogenic ones.

Autologous bone marrow-derived stem cells are, by far, the most frequently used in the latest five years of randomized and nonrandomized clinical trials in patients with myocardial infarction. Among this class, two types of stem cells have been used to date: bone marrow mesenchymal stem cells (BM-MSC) [14,15] and bone marrow mononuclear stem cells (BM-MNC) [16–18]. Their extended use relies on the ease with which they are harvested given that they do not require a donor but are obtained from myocardial infarction patients through bone marrow aspiration, and also for their ability to evade the immune system.

While most studies focus on the aforementioned cell variety, allogenic stem cells tend to gain ground in extended human studies comprising a larger number of enrolled patients, cardiac stem cells (CSC) [19], and cardiosphere derived cells (CDC) [20] being used in the latest five years of trials.

Safety over efficacy

In recent studies, both autologous and allogenic cells proved their safety (**Table 2**), with few adverse events attributed to their use. Supraventricular and ventricular premature beats were the common arrhythmic adverse findings among studies. Regarding immunogenic side effects, the CAREMI trial reported three cases of hyperpyrexia and one case of allergic dermatitis probably attributed to therapy, all of these side effects occurring in the first month after intervention. Interestingly, none of the patients experiencing these side effects had developed donor antibodies [19].

All studies in our review had efficacy as endpoint, with similar study group characteristics between trials (patients with myocardial infarction with successful primary coronary intervention with thrombolysis in myocardial infarction [TIMI] flow grade 3 and reduced left ventricular ejection fraction [LVEF] less than 45% or 40%). Only a couple studies have demonstrated an improvement in left ventricular function parameters after stem cell therapy, but both had as inclusion criteria single-vessel coronary disease, and they assessed left ventricle ejection fraction and volumes but not the infarct size, which raises the question of whether the size of the infarcted area can be inversely proportioned to the expected effect [14, 16].

The biological effect

Changes in biological parameters have been measured by both CAREMI and ALLSTAR trials and by Peregud-Pogorzelska et al., with comparable results (**Table 3**). Although the CAREMI and ALLSTAR trials did not validate an improvement in left ventricular function, they have showed changes in laboratory parameters. CRP levels have decreased more rapidly by day 7 in the study group (p=0.04) of the CAREMI trial compared to levels of CRP in the trial of Peregud-Pogorzelska. Regarding natriuretic peptides, NT-proBNP was assessed in both the CAREMI and ALLSTAR trials but only the last one proved a statistically significant difference (p=0.02) for it at follow-up (a decreasing value of -429 ± 884.1 pg/ml in study group versus -126 ± 621.5 pg/ml in control group). BNP was assessed by Peregud-Porozelska, which observed a faster decrease in the study group.

Discussion

Looking back to the early 2000s, when studies on stem cells in the cardiology field seemed to give rise to a new era with a bright outlook for a future therapy in myocardial infarction, nowadays a question is evident, with possible answers that need to be addressed: why

Table 2 - Types of stem cells and their effect in reviewed studies

CELL TYPE [ref]	END POINTS	NO. OF PATIENTS ENROLLED	TIME OF INTERVENTION	NO. OF CELLS	ASSESSMENT METHOD FOR EFFICACY	FINDINGS
Autologous BM-MNC [16]	Safety Efficacy	15 in study group, 19 in control group.	24 hours after STEMI.	8.37×10^6	LVEDV, LVESV, LVEF by echocardiography (biplane Simpson method – apical two- and four-chamber).	Achieved safety. Nine patients in study group (60%) achieved an improvement in LVEF > 10% at 12-month follow-up.
Autologous BM-MSC [14]	Safety Efficacy	14 in study group, 12 in control group.	1 month after STEMI.	$7.2 \pm 0.9 \times 10^7$	LVEF by SPECT and echocardiography.	Achieved safety. Improvement in LVEF in study group at 4-month follow-up (8.8% vs. 4.8%, p=0.031 by SPECT and 9% vs. 5.3%, p=0.023 by echocardiography).
Autologous BM-MNC [18]	Efficacy	51 in *early* study group 44 in *late* study group, 54 in control group.	*Early*: 5–7 days after STEMI *Late*: 3–4 weeks after STEMI.	$5 \times 10^7 – 5 \times 10^8$	GLS and GCS by cardiac magnetic resonance.	None of time related treatment proved an improvement in cardiac parameters.
Autologous BM-MNC [17]	Efficacy	66 in study group, 55 in control group.	6–9 days after STEMI.	100×10^6	LVEF, LVEDV, LVESV, infarct size by cardiac magnetic resonance.	Study and control group had similar results at baseline, at 6-month follow-up and between times.
Autologous BM-MSC [10]	Safety Efficacy	21 in study group, 22 in control group.	14.07 +/-9.53 days after STEMI.	$3.31 \pm 1.7 \times 10^6$	LVEF, LVEDV, LVESV by echocardiography (Simpson method) at 12 months and myocardial perfusion and metabolic activity by SPECT at 6-month follow-up.	Achieved safety. No statistically significant difference (p>0,05) between study and control group regarding LVEF, LVEDV and LVESV at 12 months or myocardial perfusion and metabolic defect index at 6-month follow-up.
Allogenic CSC [19]	Safety Efficacy	33 in study group 16 in control group.	Days 5–7 after STEMI.	35×10^6	Infarct size, LVEF, LVEDV, LVESV and wall motion score by cardiac magnetic resonance.	Safety was the primary endpoint, and it didn't reveal any major cardiac adverse events or deaths at 6- and 12-month follow-up. No significant differences in assessed parameters between the groups at baseline and follow-up times.
Allogenic CDC [20]	Safety Efficacy	90 in study group 44 in placebo group.	4 weeks to 12 months after STEMI.	2.5×10^6	Infarct size, LVEDV, LVESV, LVEF by cardiac magnetic resonance.	Safety endpoint was achieved. There was no significant difference in infarct size between groups at 6-month follow-up (p=0.51). Yet there was a reduction in LVEDV (p=0.02) and LVESV (p=0.02) at 6 month follow-up in favor of study group.

BM-MNC – bone marrow mononuclear stem cells, BM-MSC – bone marrow mesenchymal stem cells, CDC – cardiosphere derived cells, CSC – cardiac stem cells, GCS – global circumferential strain, GLS – global longitudinal strain, LVEDV – left ventricular end diastolic volume, LVEF – left ventricular ejection fraction, LVESV – left ventricular end systolic volume, SPECT – single photon emission computed tomography, STEMI – ST- segment elevation myocardial infarction

Table 3 - The biological parameter changes in trials proving the beneficial effect of stem-cell therapy in myocardial infarction

TRIAL	CELL TYPE	BIOLOGICAL PARAMETER	
Fernandez-Aviles et al., 2018 [19]	Allogenic CSC	CRP	Similar baseline values between groups. Higher levels decrease by day 7 in the study group (p=0.04). Similar values at 1-month follow-up in both groups.
		NT-proBNP	Similar baseline values. No statistically significant value at 12 months (p=0.9).
		CK and TnT	Similar decreasing trend.
Makkar et al., 2020 [20]	Allogenic CDC	NT-proBNP	Greater decreasing level at 6 months in study group (p=0.02).
Peregud-Pogorzelska et al., 2020 [16]	Autologous BM-MNC	CRP, CK-MB, TnT, BNP	Similar baseline levels between the entire study group and control group but lower CK-MB, TnT, and BNP initial values in responders, with faster decrease in BNP levels in the entire study group and TnT levels in the responders.

BM-MNC – bone marrow mononuclear stem cells, BNP – brain natriuretic peptide, CDC – cardiosphere derived cells, CK – creatine kinase, CK-MB – isoenzyme MB of creatine kinase, CRP – C reactive protein, CSC – cardiac stem cells, TnT – troponin T

the conflicting evidence in efficacy with the balance tipping to a ”no” answer?

Timing: a paramount factor in delivering stem cells to myocardial infarction patient?

There is conflicting evidence in literature of when is the best time to use stem-cell therapy in myocardial infarction. Too early treatment, hours or a few days after the event, might have no effect due to the inflammatory response in the myocardium as a response to the ischemia and necrosis, which can cause stem cell death caused by the inflammatory cells, while later therapy might be of no use due to the presence of the fibrotic scar. After acute myocardial infarction, two phases consisting of immunologic and cellular response occur, in order to create the scar. By day five a pro-inflammatory response takes place in the infarcted area, followed by an anti-inflammatory phase which peaks at day seven [21]. A study conducted in 2002 by Straurer has proved the beneficial effect of bone marrow mononuclear cells on left ventricle parameters after acute myocardial infarction. The time window used in this study was between five to nine days after infarction, suggesting that transplantation of stem cells in this period might have a hold upon the response of the left ventricle infarcted area [22].

Culprit artery: a large lesion without effect and vice versa?

The infarct size area depends on the culprit artery – the larger the vessel, the bigger the infarcted area. In trials proving the beneficial effect of stem cells, only one-vessel-disease patients were included. Occlusion of left anterior descendent artery (LAD) with anterior wall myocardial infarction was taken into consideration in both studies. In the trial from Peregud-Pogorzelska et al., out of ten patients with LAD occlusion who received stem cells by intracoronary injection, five have become responders (55.5%) with improvement in left ventricle ejection fraction, and five had no change in parameters, while among those with other vessels involved, the ratio of responders was lower (all patients with right coronary artery [RCA] occlusion responded to treatment while one out of the two patients with left circumflex [LCX] occlusion responded to treatment) [16].

The dose: a single reason for the weakness of the result?

All studies taken into consideration in our review have used different doses of stem cells (see Table), most of them numbering millions of cells. For comparison, Florea et al. proved that a dose of 25 million allogenic stem cells reduced the infarct size, but a higher dose of 100 million cells determined not just a change in size but also an improvement in left ventricle ejection fraction [23]. Yet, even if the dose of stem cells was different between trials, compared with earlier studies that included similar or lower or higher doses, a beneficial effect was not seen among all trials, probably because of the other factors that must be taken in consideration (time frame, culprit artery, cardiovascular risk factors).

Are the results comparable based on the assessment tool?

To date, studies make use of multimodality imaging for assessing the effects of stem-cell therapy in myocardial infarction, cardiac magnetic resonance becoming somewhat of a standard of assessing cardiac function in this case, yet every study used echocardiography as a comparative tool. While magnetic resonance can be considered trustworthy, echocardiography is submitted to interobserver and interobserver variability, which can be a source of error in assessing left ventricular function.

Conclusions

At the moment, trials considering therapy with stem cells in myocardial infarction are offering conflicting evidence regarding its beneficial effect on improving ventricular function. Further studies without the limitations of the present ones need to be conducted in order to have a clear view of the benefits or detriment in stem cells' potential reparatory effects.

Conflicts of Interest

none declared.

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