Original Article

Comparison of the results of the study of cellular technologies in the treatment of ischemic cardiomyopathy in different epochs of drug therapy

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ABSTRACT

Background

Currently, it is obvious that stem cell therapy opens up prospects for the treatment of certain diseases, but at the same time it faces serious problems. First, most clinical data indicate a positive effect of stem cell transplantation on heart repair, regardless of cell types and methods of their delivery.

Objectives

Comparison of the results of the study of cellular technologies in the treatment of ischemic cardiomyopathy in different epochs of drug therapy

Methods

The researched studies obtained from the PubMed and Scopus Preview databases are presented in two tables. The first table shows the studies of group "A" for the period 2004-2010.

Results

The results of the studies of the first group "A" (2004-2010) were as follows: in studies like T. Siminiak et al. (2004), N.Dib et al. (2005), A.A. Hagege et al. (2006), M. Haack- Sorensen et al. (2008) (MSC-HF), Hare J.M. et al. (2009), Assmus B. et al. (2010), Strauer B.E. et al. (2010) (STAR- heart research); Wang S. and co-author. (2010), Mansour S. et al. (2010) (COMPARE-AMI study) stem cells used in ischemic cardiomyopathy had a positive effect on the myocardium.

Conclusion

The results of the analysis of the studies showed the following: given the changes in the tactics of drug therapy of CHF over time, there was no significant difference in the results between the two groups of studies on the use of stem cells in ischemic cardiomyopathy.

Keywords

Comparison, cellular technologies, cardiomyopathy, drug therapy.

INTRODUCTION

Currently, it is obvious that stem cell therapy opens up prospects for the treatment of certain diseases, but at the same time it faces serious problems. First, most clinical data indicate a positive effect of stem cell transplantation on

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DOI: https://doi.org/10.3329/bjms.v24i2.81724

heart repair, regardless of cell types and methods of their delivery. Secondly, the results of stem cell therapy in ischemic cardiomyopathy (ICMP) are characterized by significant variability: from mild to moderate or contradictory results in relation to the function and structure of the left ventricle (LV), and improvements are often short- term. Thirdly, some types of stem cells and their delivery methods have been associated with serious adverse effects, such as cardiac arrhythmias and vascular restenosis, which requires immediate attention from researchers and clinicians. Several important factors affecting the effectiveness of stem cell infusion in patients with ICMP and myocardial infarction (MI) include the method of delivery, the type and number of stem cells, the viability of these cells, as well as the patient's health status, as there are studies comparing stem cells of patients and healthy people [1-3]. All these factors have been examined in detail by certain experts, and our discussion focuses on other factors that may affect stem cell therapy. This is the role of drugs that change over time due to advances in stem cell therapy in patients with ischemic cardiomyopathy. The 20 studies we are studying are divided into 2 groups: in the first group of the study, 10 studies were studied in which stem cells were used for the treatment of ICMP conducted in the period 2004-2010, and in the second group 10 studies of stem cell therapy for ICMP conducted in the period 2015-2021. We compared the results of studies between the groups, taking into account changes in the tactics of drug therapy of CHF over time. For example, in the period from 2004 to 2010, the National Recommendations for the diagnosis and treatment of CHF in 2003, 2006 were used as a basis for the treatment of CHF, and in the period from 2015 to 2021, the clinical protocols for the diagnosis and treatment of CHF of the Ministry of Health of the Republic of Kazakhstan from 2013, revised from 2018 and from 2020 were used.

INTRODUCTION

Currently, it is obvious that stem cell therapy opens up prospects for the treatment of certain diseases, but at the same time it faces serious problems. First, most clinical data indicate a positive effect of stem cell transplantation on heart repair, regardless of cell types and methods of their delivery. Secondly, the results of stem cell therapy in ischemic cardiomyopathy (ICMP) are characterized by significant variability: from mild to moderate or contradictory results in relation to the function and structure of the left ventricle (LV), and improvements are often short-term. Thirdly, some types of stem cells and their delivery methods have been associated with serious adverse effects, such as cardiac arrhythmias and vascular restenosis, which requires immediate attention from researchers and clinicians [3]. Several important factors affecting the effectiveness of stem cell infusion in patients with ICMP and myocardial infarction (MI) include the method of delivery, the type and number of stem cells, the viability of these cells, as well as the patient's health status, as there are studies comparing stem cells of patients and healthy people [1,2]. All these factors have been examined in detail by certain experts, and our discussion focuses on other factors that may affect stem cell therapy. This is the role of drugs that change over time due to advances in stem cell therapy in patients with ischemic cardiomyopathy. The 20 studies we are studying are divided into 2 groups: in the first group of the study, 10 studies were studied in which stem cells were used for the treatment of ICMP conducted in the period 2004-2010, and in the second group 10 studies of stem cell therapy for ICMP conducted in the period 2015-2021. We compared the results of studies between the groups, taking into account changes in the tactics of drug therapy of CHF over time. For example, in the period from 2004 to 2010, the National Recommendations for the diagnosis and treatment of CHF in 2003, 2006 were used as a basis for the treatment of CHF, and in the period from 2015 to 2021, the clinical protocols for the diagnosis and treatment of CHF of the Ministry of Health of the Republic of Kazakhstan from 2013, revised from 2018 and from 2020 were used.

METHODS

The researched studies obtained from the PubMed and Scopus Preview databases are presented in two tables. The first table shows the studies of group "A" for the period 2004-2010. The first column contains the name of the study, the author and the year of the study, the second column indicates the category of patients with certain heart parameters, and the third column presents a brief result of the study describing the effect of the use of stem cells on the parameters of cardiac activity or its absence (see Table No. 1). The second table shows the studies of group "B" conducted during the period 2015-2021 (see Table No. 2).

Table No. 1. Group A studies conducted from 2004 to 2010.

No	Research, year	The patients category with specific heart drugs	Impact
1	T. Siminiakand co-authors., 2004, Poland (n=10) [4]	Left ventricular ejection fraction (LVEF) 25-40%, suffered myocardial infarction (MI).	Improved LVEF; reduced risk of ventricular arrhythmia
2	N.Dib and co-authors., 2005, USA (n=24) [4]	LVLF <40%, transferred by HIM.	Increased areas of metabolically active myocardium; reduced risk of ventricular arrhythmia
3	A.A. Hagege and co-authors., 2006, France (n=9) [4]	LVLF <35%, transferred by HIM.	Improvement of LVL; reduction of HF FC and the risk of developing ventricular arrhythmia
4	P.Menasche and co-authors., 2008 (MAGIC), France (n=97) [4]	LVLF <35%, transferred by HIM.	There was no improvement in the functional state of LV compared to the control group
5	M. Haack-Sorensen and co-authors., 2008. (Research MSC-HF) (n=60) [5]	Patients with chronic ischemic heart failure	Significant improvement in LV systolic myocardial function (CSR, LVLF)
6	Hare J.M. and co-authors., 2009. (n=53) [6]	Patients with MI (LVEF – 30-60%)	Safe intravenous injection of stem cells after acute myocardial infarction
7	Assmus B. и and co-authors.,2010. (n=204) [7]	Patients after myocardial infarction reperfusion	Improvement of regional contractility and LV function; reduction of major adverse events.
8	Strauer B.E. and co-authors., 2010. (Research STAR-heart) (n=391) [8]	Patients with chronic HF on the background of ICMP, LVEF < 35%	Increased LVEF and physical load tolerance, improved LV contractility; reduced mortality; Improved quality of life.
9	Wang S. and co-authors ., 2010. (n=112) [9]	Refractory angina pectoris, FC III–IV.	Reduction of the frequency of angina attacks, improvement of physical load tolerance; safety is noted
10	Mansour S. and co-authors., 2010. (Research COMPARE-AMI)(n=14) [10]	Patients with postoperative LVH <50%	Improvement of LV function (increased LVEF), safety and effectiveness are noted

Table No.2. Studies of the "B" group conducted from 2015 to 2021.

No	Research, year	Initial parameters of the heart	Impact
1	Chullikana A. and co-authors., 2015. (n=20) [11]	of patients after percutaneous coronary intervention (PCI) on THEM with ST elevation	The use of stem cells was noted for its safety and the absence of adverse events when administered intravenously to patients with AMI 2 days after PCI.
2	Mathiasen A.B. and co-authors., 2015. (Research MSC-HF) (n=60) [12]	patients with HF on the background of ICMP LVLJ <45%	Intramyocardial injection of autologous stem cells proved safe and improved myocardial function in patients with severe ischemic heart failure.
3	Aliya Dzholdasbekova and co-authors	patients with chronic heart failure (EF <45%)	A decrease in the size of the LV cavity, an improvement in the myocardial histological function, and a decrease in the functional class of CHF.
4	Guijarro D. and co-authors., 2016. (Pilot Research MESAMI 1) (n=10) [14]	patients with ICMP, LVLH < 35%	The safety of stem cell therapy with potential improvement of cardiac function, LV remodeling and improvement of functional indicators (6-minute walk test and NYHA CH class) was noted.
5	Florea V. and co-authors., 2017. (Research TRIDENT) (n=30) [1]	Patients with ICMP.	Stem cells, when used in large and small doses, reduced the size of scar tissue, while a high dose increased
6	Bartolucci J. and co-authors., 2017. (Research RIMECARD) (n=30) [2]	LVL in patients with CHF with reduced LV with optimal therapy	Intravenous administration of mesenchymal stem cells was found to be safe. There was an improvement in LV myocardial function, functional class (FC) and quality of life.

No	Research, year	Initial parameters of the heart	Impact
7	Qayyum A.A. and co-authors., 2017. (Research MyStromalCell)(n=60) [15]	patients with HF FC II-III (CCS/NYHA), LVEF> 40% and with single-digit coronary artery stenosis.	Stem cell treatment was safe. It did not improve physical load tolerance compared to the placebo group.
8	Bartunek J. and co-authors., 2017. (Clinical Research CHART-1) (n=240) [16]	patients with CHF on the background of ICMP, with reduced LVEF (<35%) and at high risk of SCD, despite optimal drug therapy (OMT).	The use of autologous stem cells has shown efficacy and safety in the treatment of CHF against the background of ICMP.
9	Yau T.M. and co-authors., 2019. (n=159) [17]	patients with end-stage HF	There was no improvement in the restoration of LV function. The annual mortality rate did not differ significantly between the group that received stem cells and the neutron group; the frequency of repeated hospitalizations did not differ significantly between the study groups.
10	Ostovaneh M.R. and co-authors., 2021. (Clinical Research ALLSTAR) (n=142) [18]	patients with LVF <45%	led to an improvement in segmental function of the LV myocardium containing scar tissue relative to the placebo group.

RESULTS

The results of the studies of the first group "A" (2004-2010) were as follows: in studies like T. Siminiak et al. (2004), N.Dib et al. (2005), A.A. Hagege et al. (2006), M. Haack-Sorensen et al. (2008) (MSC-HF), Hare J.M. et al. (2009), Assmus B. et al. (2010), Strauer B.E. et al. (2010) (STAR-heart research); Wang S. and co-author. (2010), Mansour S. et al. (2010) (COMPARE-AMI study) stem cells used in ischemic cardiomyopathy had a positive effect on the myocardium. There was an improvement in the systolic function of the left ventricle, increased exercise tolerance, improved quality of life, decreased the frequency of angina attacks and the risk of ventricular arrhythmia. Thus, out of 10 studies conducted between 2004 and 2010, 9 studies of the use of stem cells in ICMP showed a positive effect and safety. Only in one study by P.Menasche et al., 2008 (the MAGIC study), there was no improvement in LV myocardial function compared with the control group. The results of the studies of the second group "B" for the period 2015-2021 showed the following: studies such as Chullikana A. and co-author. (2015), Mathiasen A.B. et al. (2015) (MSC-HF), Aliya Dzholdasbekova et al. (2015, Kazakhstan), Guijarro D. and co-author. (2016) (MESAMI pilot study 1), Florea V. and co-author. (2017) (TRIDENT research), Bartolucci J. and co-author. (2017) (RIMECARD study), Bartunek J. and co-author. (2017) (clinical study CHART-1), as well as Ostovaneh M.R. et al. (2021) (ALLSTAR clinical trial) showed that the use of stem cells in the treatment of ischemic cardiomyopathy (ICMP) led to an improvement in the systolic function of the left ventricle and a decrease in the functional class of chronic heart failure (CHF). In these studies, the positive effect of stem cells on the parameters of cardiac activity was noted in 8 out of 10 cases. However, in two studies (conducted between 2015 and 2021) – a study by Qayyum A.A. et al. (2017) (a study by MyStromalCell) and Yau T.M. et al. (2019) – there was no improvement in the recovery of the left ventricle. Annual mortality did not differ significantly between the groups receiving stem cells and the control group. The frequency of repeated hospitalizations also did not differ between the study groups, and there was no improvement in exercise tolerance compared with placebo.

DISCUSSION

Before discussing the results of the above 20 studies, I would like to focus on the concept of the "era" of medicines. In order to present the concept of the epochs of drug therapy of CHF, we will discuss a little the "old" and "new" tactics of CHF management. After reading the standard treatment protocol for CHF, you may not notice this. Drug therapy of heart failure, as in other nosologies, does not stand still and undergoes changes over time. The "changes" relate not only to the emergence of new groups of drugs, but also to the revision of their dosages, multiplicity and combinations of existing drugs, due to the emergence of new data on effects in clinical practice and research. For example, in the treatment of CHF in 2006, groups of drugs such as i-ACE, BAB were recommended for CHF I and II FC

(NYHA), and diuretic drugs were recommended only for FC II (with a stagnation clinic), including thiazide diuretic drugs in small doses (hydrochlorothiazide 12.5–50 mg/day.). In FC III (in the decompensation stage), loop (thiazide) diuretics in combination with aldosterone antagonists in high doses (150-300 mg, once in the morning or twice in the morning and at lunch) were recommended for 2-3 weeks before achieving HF compensation. To maintain the condition at III FC, combination therapy was recommended: loop diuretics in small doses + spironolactone in small doses (25-50 mg / day). In case of IV FC, a combination of loop and thiazide diuretics (for example, metolazone), an aldosterone antagonist, and a carbonic anhydrase inhibitor was recommended (diacarb 0.5g x 3 times a day for 2-3 days, then once every 3 weeks, to maintain acid-base balance and increase sensitivity to diuretic drugs) [19]. After 2013, the tactics of CHF treatment changed towards prevention. For example, decongestant therapy begins earlier than stagnant phenomena occur (for example, the use of mineralocorticoid receptor antagonists such as eplerenone at a dose of 25-50 mg / day at II FC), which helps to protect organs from stagnant processes. In the updated protocols for the treatment of CHF, the strategy for the use of cardiac glycosides has also changed. For example, from the group of cardiac glycosides, only digoxin is recommended for the treatment of HF with low LV and atrial fibrillation with accelerated ventricular rate (VHF), when it is not possible to use other therapy options. While in the "old" approaches to the treatment of CHF, cardiac glycosides were the drug of choice for atrial fibrillation, and in small doses were used with caution even with sinus rhythm [20]. So, as a result of the analysis of the studies of groups "A" and "B", the following was obtained: in the first group of studies (2004-2010), 9 out of 10 studies showed a positive effect when using stem cells, in one study there was no effect. In the studies of the second group (2015-2021), 8 out of 10 studies showed a positive effect from the use of stem cells in ICMP, and in two studies no effect was observed.

CONCLUSION

The results of the analysis of the studies showed the following: given the changes in the tactics of drug therapy of CHF over time, there was no significant difference in the results between the two groups of studies on the use of stem cells in ischemic cardiomyopathy. To determine and evaluate the effect of drug changes on the treatment of ischemic cardiomyopathy with stem cells, special studies are required to study this issue in more depth.

Source of fund: (if any).

No funding

Conflict of Interest: No Conflict of interest

Ethical clearence: Not Applicable

Authors's contribution

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