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Novel Treatment Measures of Acute Myocardial Infarction: A Review

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Abstract: Myocardial infarction is the leading cause of congestive heart failure and death in most developed and developing countries. This review focuses on novel treatment methods like stem cell therapy and nutritional factors projecting towards treatment of acute myocardial infarction. Stem cell therapy for conditions characterized by myocyte loss in myocardial infarction and heart failure is intuitively appealing. Stem cell therapy, initially introduced as a novel approach to regenerate injured cardiac myocytes, has now been widely gaining popularity as a feasible strategy for repairing injured myocardial muscle tissue. In certain cases inefficient cellular metabolism and blood borne nutrients is important factor in determining whether cardiac pathology will develop or not. Metabolic dysfunction could result from intracellular deficiencies of magnesium, coenzyme Q_{10}, carnitine and certain B vitamins, nutrients which play a role in synthesis of ATP. Nutritional treatment is potentially effective for treatment of MI due to inefficient cellular metabolism and their antioxidant property helps in improving the outcomes in patients with acute MI. Magnesium, L-carnitine, Vitamin C, Vitamin E and other B Vitamins when clinically tested showed substantial reduction in death rate in early stages of acute MI.

Key words: Myocardial Infarction · Stem Cell Therapy · Cardiac Myocyte · Vitamin B · Magnesium · L-Carnitine

INTRODUCTION

Acute myocardial infarction (AMI) is one of the leading causes for death worldwide and it is the single largest cause of death in the United States, responsible for 1 out of every 6 deaths [1, 2]. Many patients with acute MI have been saved by recent treatment advances, but many of these same patients then suffer from ischemic heart failure. Heart transplantation provides hope for those patients with end-stage heart failure who have failed to respond to conventional therapies. Yet, a shortage of donors and the potential of post-operative complications, such as transplant vasculopathy and allograft rejection, limit the feasibility of heart transplantation [3]. With research advances in stem cell biology and regenerative medicine, including tissue engineering and cell therapy, it is hoped that in the near future stem cell transplantation will be a promising treatment modality for patients with ischemic heart failure. Pathophysiologically, post-MI heart failure is characterized by irreversible loss of cardiomyocytes which leads to progressive functional deterioration. It is hoped that stem cell transplantation, by providing a potential source of new cells with its multipotent characteristics, will hold promise for patients with ischemic heart failure. The present review is aimed to increase clinicians' understanding of stem cells and their therapeutic potential as well as use of specific nutrients for treatment of cardiovascular disease, with particular focus on MI.

Stem Cell Therapy in Acute Myocardial Infarction: Stem cells are primitive, undifferentiated; undefined pluripotent multilineage cells that retain the ability to renew themselves through mitotic cell division and can divide and develop a cell more differentiated than it. Every single cell in the body originates from this type of cell. They are obtained from embryo and fetus as well as from various parts of the adult body. Multiple tissues have been shown to contain organ-specific progenitor

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cells. Stem cells are usually classified according to the following criteria: origin, type of organ or tissue from which the cells are derived, surface markers and final differentiation fate [4]. Many animals like planarian plat worms and amphibians have the ability to regrow lost body parts with speed and precision through a process called regeneration. Salamanders can regenerate lost body parts [5], like a limb, by dedifferentiation of specialized cells into stem cells which proliferates and eventually differentiate into the specialized cells of the regenerated organ. Zebrafish are capable to regenerate their heart completely [6].

Humans have lost most of their regenerative capacity, except for wound healing and liver regeneration after partial hepatectomy. The human heart was always thought to be a terminally differentiated organ, but about ten years ago it became clear that cardiomyocytes can divide [7]. It was cleared that this even can happen after a myocardial infarction [8]. The hope that patients who suffer from myocardial infarction can be treated with stem cells is based on remarkable regeneration ability of animals [9], on observations of bone marrow transplants in patients suffering from leukemia and on the recently discovered plasticity of the human heart. The presence of donor bone marrow cells in the hearts of patients that underwent bone marrow transplantation [10] suggested that bone marrow might play a role in repairing the myocardium and vasculature.**Types of Stem Cells**

Most clinical studies used unfractionated bone marrow cells as the delivery product, postulating that stem and progenitor cells within these cells are the biologically relevant therapeutic agents [11]. However, it is the embryonic stem cells and induced pluripotent stem cells which are the only cell types that currently have the potential to generate bona fide cardiomyocytes on a scale that potentially replace the cells lost in AMI [12]. Stem cells are classified as autologous or allogenic, depending on their origin. Allogenic cells have promising option for stem cell therapy, provided they are free from the immunogenic complications and also the risks of malignancy.

Embryonic Stem Cells: Embryonic stem cells (ESC) are derived from the blastocyst of human embryos prior to implantation and possess the capability to get differentiated into any cell from the three germ lines, one of which is cardiac myocytes. However, due to the inherent totipotency of these cells can also predispose to tumor formation including teratomas, which have been observed in animal models [13]. Additionally, there is controversy surrounding the ethical issues of ESC use [14]. Human umbilical cord blood cells contains a large number of non-hematopoietic stem cells which rarely express human leukocyte antigen (HLA) class II antigens and appear to be immunologically naive, thus reducing the risk of rejection. In animal models of AMI injection of human umbilical cord blood cell (hUCBC) is associated with significant reductions in infarct size, particularly when administered by the intra-myocardial route [15].

Induced Pluripotent Stem Cells: Induced pluripotent stem cells (iPSC) may be developed by fully differentiated somatic cells by genetic reprogramming, hence resulting in a fully undifferentiated ESC-like phenotype, capable of *in-vitro* proliferation and differentiation towards cells from all three germ layers [16]. Moreover, these cells are obtained from the patient's own skin fibroblasts, thereby alleviating any immunological discord.

Resident Cardiac Stem Cells: These cells have the potential to differentiate into different lineages like vascular smooth muscle and myocardial cells and studied in animal models of myocardial infarction resulting in beneficial outcomes in terms of reducing infarct size and improving LV function [17].

Adipose and Skeletal Muscle Derived Stem Cells: Adipose derived stem cells (ASC) are easy to obtained through liposuction and contain, in addition to mesenchymal elements, hematopoietic and endothelial cell lines. Preclinical studies showed that ASC have been associated with improvement in ejection fraction in animal models of myocardial infarction and neo-angiogenesis via paracrine factors [18]. Skeletal muscle cells are harvested by muscle biopsy from the index patient, thereby mitigating any immunogenicity issues. Preclinical animal studies have demonstrated the ability for skeletal myoblasts to engraft, form myotubules and enhance cardiac function after transplantation into infarcted myocardium [19].

Bone Marrow Derived Stem Cells: Bone marrow stem cell has been the widely studied, after a landmark trial published by Orlic *et al*. which demonstrated that bone marrow cells regenerate infarcted myocardium in mouse models [20]. The transplanted cells undergo trans-differentiation into cardiomyocytes with newly formed myocardium occupying a significant proportion of the infarcted area with significant improvement in the left ventricular ejection fraction (LVEF) just nine days after

cell transplantation. Furthermore, bone marrow cells (BMC) transplanted into rats following left anterior descending (LAD) artery ligation improved cardiac function and induces angiogenesis, by formation of new capillaries positive for human markers [21].

Experimental data suggested that stem cells from the mononuclear fraction of BMC undergo trans-differentiation, a process by which they differentiate into other cell lineages, including cardiomyocytes.

Mechanism of Action: For producing a therapeutic response, stem cells need to home to the injured myocardium, adhere to and transmigrate through the endothelium, invade the interstitium and finally engraft the damaged myocardium [12]. MI causes loss of functional myocardium due to hypoxic necrosis, inflammatory change and cardiomyocyte apoptosis. Apart from progressing through different stages of inflammation and healing, the dynamic microenvironment in the infarction zone also express cardiac cytokines that promotes stem cell migration and homing [22]. Transplanting stem cells to the post-infarct myocardium intensify the cytokine effect to attract endogenous stem cells. Various paracrines secreted by stem cells thought to have therapeutic effect by promoting angiogenesis, proliferation of endogenous vascular cells, loosening of fibrotic extracellular matrix, inhibition of cardiomyocyte apoptosis and regulation of inflammatory response. Altogether the paracrine signals from stem cells expedite wound healing and promote the endogenous myocardial regeneration process [23]. Apart from paracrine signaling effects, stem cells carry the potential to differentiate into functional myocardium [24]. The supplementation of exogenous stem cell post-MI can engraft into the existing myocardium as functional cardiomyocyte that beats in synchronously with the existing myocardium. Stem cells can also differentiate into smooth muscle cells and vascular endothelial cells. Together, the delivery and differentiation of stem cells replenishes the lost cardiomyocytes from MI and provides increased vascularity in the post-injury zone to prevent further ischemic tissue damage [25].

Human Clinical Trials: Although, multiple experimental animal models and clinical trials of cell-based cardiac therapy have delivered promising results, but still the mechanisms of their effect are unclear [26]. The majority of large clinical trials used bone marrow stem cells alone, but some trials also aimed at two populations. The TOPCARE AMI [27], REGENT [28] and HEBE [29] trials were those that used a second cell line in addition to BMCs. Commonly stem cells were delivered via intracoronary injection and some of the parameters that assessed for significance were, increase in left ventricular ejection fraction, decrease in end systolic and end diastolic volumes and reduction in infarct size. These parameters were measured by LV angiography, MRI, SPECT or 2D echocardiography. The major clinical trials that have shown a benefit in the group given stem cell therapy over the control group are summarized in Table 1:

Cardio-Protective Nutrients

Magnesium: Magnesium shows a number of effects that would be beneficial in the treatment of AMI. Magnesium inhibits platelet aggregation and platelet dependent thrombosis [40], promotes vasodilation and prevents vasospasm [41] and has antiarrthymic activity. Also by acting as a cofactor in the synthesis of ATP, magnesium plays a major role in myocardial energy production. Catecholamines released during various types of stress causes loss of magnesium from the heart and increase urinary magnesium excretion. Magnesium deficiency in turn increase the amount of catecholamines released in response to stress and aggravates the cardiotoxic effects of adrenaline thereby creating a vicious cycle of greater magnesium deficiency and an increasing deleterious response to stress [42, 43]. Ischaemia also causes a loss of magnesium from myocardial tissue [44], potentially increasing the vulnerability of the myocardium to the adverse effects of ischemia.

Myocardial necrosis induced in rats by restraint stress was also reduced by intraperitoneal administration of potassium-magnesium aspartate [45]. In addition cardiac necrosis induced in rats by injection of epinephrine were exacerbated by magnesium deficiency and decreased by magnesium supplementation [46]. Magnesium deficiency increased the size of myocardial infarcts induced by surgical occlusion of the left anterior descending artery for one hour [47] in dogs. In another experiment in rats fed a standard diet and subjected to surgical occlusion of the left coronary artery, MI occurred in 100 percent of 16 animals. Magnesium chloride (p.o) for 5 days prior to surgical occlusion reduced the incidence of infarction to 29% [48].

Magnesium deficiency (in intravenous load test) was found to be common in patients with ischaemic heart disease [49]. In addition serum magnesium levels were significantly lower in patients hospitalized with an acute MI than in other hospitalized patients. The risk of developing cardiac arrhythymias during an acute MI was

Table 1: Major Clinical Trials

Trial Name and Design	Cell Line	Sample Size (n)	Days to Cell Dose*	Admin Post MI*	Route of Admin	Imaging Modality	Primary End Point
TOPCARE-AMI [30] (2002)	BMC OR CPC	59	BMC: 2.13±75 × 10^{8*} CPC: 0.16±12 × 10^{8*}	4.9±1.5*	IC	LV angiogram MRI	● Increased LVEF ● Decreased ESV ●Reduced infarct size (4 months and 1 year)
BOOST [31] (RCT 2004)	BMC	60	24.6±9.4 × 10^{8*}	4.8±1.3*	IC	MRI	● Increased LVEF by 6% over control (At 6 months)
REPAIR-AMI [32] (RCT 2006)	BMC	204	2.4±1.7 × 10^{8*}	4.3±1.3*	IC	LV angiogram	● Increased LVEF by 2.5% over control (At 4 months)
FINCELL [33] (RCT 2008)	BMC	80	3.6 × 10^{8} (median)	2-6	IC	LV angiogram	● Increased LVEF by 5% over control (At 6 months)
LEUVEN-AMI [34] (RCT 2006)	BMC	67	3.0±1.3 × 10^{8*}	<24 hours	IC	MRI	●No increase in EF over control (At 4 months) ●Possible decrease in infarct size
ASTAMI [35] (RCT 2006)	BMC	100	0.68 × 10^{8} (median)	6 ± 1*	IC	SPECT	● No increase in EF over control (At 6 months)
REGENT [36] (RCT 2009)	BMC or CD34/CXCR4	200	BMC: 1.78× 10^{8} (median) CD34/CXCR4: 0.019 × 10^{8} (median)	3-12	IC	MRI	● No increase in EF over control
HEBE [37] (RCT 2010)	BMC or mPBC	200	BMC: 3±1.6× 10^{8*} mPBC: 2.9±1.4× 10^{8*}	3-8	IC	MRI	● No increase in EF over control (At 4 months)
BONAMI [38] (RCT 2009)	BMC	101	0.98±0.09 × 10^{8*}	9.3±1.7*	IC	SPECT RNA MRI ECHO	● No increase in EF over control ● No decrease in infarct size (At 3 months)
CADUCEUS [39] (RCT 2012)	CDC	31	12.5-25 × 10^{6}	1.5-3 mths	IC	MRI	● No increase in EF over control (At 6 months)

*All values are mean ± SD unless stated

Abbreviations: TOPCARE-AMI Trial: Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction Trial; REPAIR-AMI Trial: Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction Trial; BOOST Trial: Intracoronary autologous bone-marrow cell transfer after myocardial infarction; RCT: Randomized control trial; ASTAMI Trial: Autologous Stem cell Transplantation in Acute Myocardial Infarction Trial; REGENT Trial: Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction Trial; HEBE Trial: Intracoronary infusion of autologous mononuclear bone marrow cells or peripheral mononuclear blood cells after primary PCI Trial; BONAMI Trial: Bone Marrow in Acute Myocardial Infarction Trial; CADUCEUS Trial: Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction trial; MRI: Magnetic resonance imaging, SPECT: Single Photon Emission Computed Tomography; CPC: Cardiac progenitor cell; LVESV: Left ventricular end systolic volume; PBC: Peripheral blood cell; RNA: Radionuclide angiography, CDC: Cardiosphere derived cell.

significantly greater in hypomagnesemic than in normomagnesemic patients [50]. The number of evidences indicates parenteral administration of appropriate doses of magnesium markedly decrease and improve other clinical outcomes in patients with acute MI.

L-Carnitine: Carnitine plays a role in myocardial energy production by facilitating the transport of fatty acids into mitochondria. Myocardial carnitine depletion occurs during ischemia and so low carnitine levels might exacerbate ischemia and contribute to pathogenesis of MI. In rats carnitine administration protected against the development of infarct like myocardial necrosis induced by isoprenaline [51]. Low carnitine concentrations have been found in necrotic areas of myocardium of patients who had an acute MI, whereas carnitine levels were normal in surrounding healthy myocardial tissue while carnitine concentrations were intermediate in the border zone between necrotic and healthy tissue, possibly indicating an area of reversible metabolic injury for which restoration of adequate carnitine levels might be useful [52].

During clinical trials treatment with L-carnitine significantly decreased the levels of creatine kinase-MB and troponine-I (markers of cardiac injury) and reduced the incidence of ventricular arrhythmias in patients with acute MI and reduces the incidence of death and heart failure following acute MI and increased survival in patients suffering from cardiogenic shock.

Vitamin E and C: An increased oxidative stress arises during an acute MI and after reperfusion with a fibrinolytic agent. This increase in oxidative stress may contribute to the pathogenesis of both MI-related myocardial damage and reperfusion injury [53-55]. Because vitamins E and C have antioxidant activity they might minimize free radical-induced myocardial damage. Blood and leukocyte levels of vitamin C are reported to fall significantly during the hours and first several days following an acute MI [56, 57].

Vitamin E occurs naturally in food and consists of four isomers: alpha-, beta-, gamma- and delta-tocopherol and is preferable to administer Vit.E as mixed tocopherol. Human studies have shown supplementation with alpha-tocopherol can deplete gamma-tocopherol [58] and there is evidence that gamma-tocopherol is as important as alpha-tocopherol for cardiovascular disease prevention. For e.g, gamma-tocopherol is effective than alpha-tocopherol for scavenging peroxynitrite and other nitric oxide-derived oxidants [59, 60] which appear to be inflammatory mediators that promote the development of atherosclerosis. In addition gamma-tocopherol may be a more potent anti-inflammatory agent than alpha-tocopherol since it inhibits cyclooxygenase-2 activity at a concentration at which alpha-tocopherol has no effect [61]. Furthermore a metabolite of gamma-tocopherol functions as a natriuretic hormone [62] and as such may help prevent the development of heart failure.

B vitamins: Several different B vitamins play a role in myocardial energy production and therefore might be useful in reducing myocardial vulnerability to ischemia. The mean plasma concentration of pyridoxal phosphate (the biologically active form of vitamin B6) decreased by 50% during the acute phase of an MI and returned to normal before discharge from the hospital [63, 64].

Concluding Remarks: The evidence reviewed in this article suggests that parenteral administration of magnesium in the setting of an acute myocardial infarction could greatly decrease the death rate from this disease. In addition several clinical trials have shown that L-carntitine, vitamin C and vitamin E are beneficial in the treatment of acute MI. B vitamins are also beneficial and warrant further research. This review article will be useful for clinicians and researchers for futuristic development of medicines.

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