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Review

Collagen–Based Hydrogel Encapsulated Cardiosphere–Derived Cell (CDC): Potential of Stem Cells as Tissue Repair Therapy Post–Acute Myocardial Infarction.

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Abstract

Background: Acute myocardial infarction (AMI) is a global health issue that is the leading cause of morbidity and mortality. Post-AMI management currently has therapeutic and side-effect limitations and has not been able to repair damage to myocardial tissue caused by AMI. The development and discovery of therapeutic modalities with the potential for a more optimal therapeutic effect remains a challenge in this post-AMI treatment. The purpose of this literature review is to collect and analyze various sources related to collagen-based hydrogel encapsulated cardiosphere-derived cells (CDC). This literature review is written systematically by gathering library sources from various databases, such as Google Scholar, PubMed, and Research Gate. According to the findings of the study, the CDC has the potential to be used as a post-AMI therapy because it can promote regeneration of the heart, which has lost function as a result of the AMI. To achieve the greatest effect, this modality is administered intracoronary. This treatment will be encapsulated with collagen hydrogel, which has a cardioprotective effect, to increase the survival and effectiveness of CDC. The use of collagen-based hydrogel encapsulated CDC can provide post-AMI cell regeneration effects comparable to existing modalities while having minimal side effects. Further investigation in larger and more definitive trials is needed to elucidate the potential use of CDC therapy in AMI.

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Keywords: *acute myocardial infarction, cardiosphere-derived cell, collagen, hydrogel.*

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Introduction

Acute myocardial infarction (AMI), commonly referred to as a heart attack, is one of the main causes of morbidity and mortality that is still a global challenge. AMI is commonly caused by a decrease or cessation of blood flow to parts of the heart, resulting in heart muscle necrosis.[1] This condition causes more than 15% of deaths each year.[2] Ischemic heart disease also remains the number one cause of death and illness in Indonesia with the number of disability-adjusted life years (DALYs) increasing by 10.5% from 5.9 million in 2006 to 6.52 million in 2016.[3]

As secondary prevention, patients who had suffered AMI were given a variety of therapies, both pharmacological and non-pharmacological. To reduce mortality and cardiovascular morbidity, patients were given aspirin, β blockers, statins, and angiotensin-converting enzyme inhibitors (ACEi). Lifestyle modification and cardiac rehabilitation are also recommended for this group of patients. This group of therapy is an ongoing and lifelong process that allows the patient to return to a normal life.[4] The complexity and side effects of this treatment regimen can reduce patient compliance, resulting in a poor outcome. This modality is also less effective because it doesn't repair tissue damage caused by AMI.[5]

Research shows that cardiosphere-derived cells (CDC) have the potential to be used as post-AMI therapy.[6] These cells can promote heart regeneration, reduce scarring, and improve heart function.[7] CDC also provide advantages such as improved cardiac function, faster cell turnover, increased myogenic differentiation, improved cardiac morphology, and lowered apoptosis of cells when compared to stem cells derived from bone marrow or adipose.[8] This modality must be administered correctly for CDC to reside in infarcted tissue and provide a long-lasting therapeutic effect. The CDC will achieve consistent therapeutic success and effectiveness with good cell retention. The use of biomaterials can improve cell retention at the infarct site.[9]

Biomaterials can act as an extracellular matrix replacement for encapsulated cells thereby increasing cellular viability of the cells. This biomaterial aids in the delivery of more cells to the target site, the maintenance of cell localization and viability, and the enhancement of the continuous production of beneficial paracrine factors at the target site. One of the biomaterial approaches that can be provided to achieve cellular delivery to the myocardium is a collagen-based hydrogel. Collagen itself is the main component of the myocardial extracellular matrix, so the administration of collagen-based hydrogel can support the attachment and elongation of cardiomyocytes. Based on the description above, the collagen-based hydrogel encapsulated CDC injection approach has the potential to be used as a tissue repair therapy in post-myocardial infarct conditions.[9–11] This literature review aims to discuss the potential use of collagen-based hydrogel encapsulated CDC as a post-AMI tissue repair therapeutic modality. The authors hope that this review can provide a new theoretical basis for treating post-myocardial infarction patients.

Methods

This review is prepared using the literature synthesis method. The literature was searched using the keywords "*acute myocardial infarction*", "*cardiosphere-derived cell*", "*collagen*", "*hydrogel*" and "*collagen-based hydrogel*" on numerous electrical databases—ScienceDirect, PubMed, and Research Gate— from inception up to August 2024, without imposing any restrictions on publication years. There are 52 relevant and appropriate publications. Information from these sources is reviewed, analyzed, and compiled into a comprehensive scientific literature review.

Results and Discussion

Pathogenesis of Acute Myocardial Infarction (AMI)

Myocardial infarction (MI) begins with the accumulation or blockage of atherosclerotic plaques in the coronary arteries, which supply blood to the myocardial muscle. Chronic endothelial injury caused by cardiovascular risk factors such as chronic hyperlipidemia, long-term hypertension, or smoking initiates atherosclerosis. This process starts at a young age and takes a long time to cause significant obstructions. Due to hemodynamic disturbances, this plaque can rupture, fissure, or ulcerate, and the body responds by

Table 1. The role of CDC as a therapeutic agent for cardiac tissue repair.[18,19,24–26]

CDC's Multiple Roles in Cardiac Regeneration
- Myogenesis
- Cardiogenesis
- Angiogenesis
- Improved cell engraftment
- Releases paracrine factors
- Prolongs the survival of cardiomyocytes
- Activates endogenous cardiac stem cells
- Mediates the process of scar reduction due to myocardial infarction
- Increases capillary density
- Improve work function and improve heart morphology
- Stops detrimental tissue reconstruction
- Increase the differentiation of heart cells
- Mediates the process of reducing fibrosis
- Secretes pro-angiogenic and pro-cardiogenic cytokines
- Increase myogenic differentiation
- Reducing the levels of apoptotic cells

forming a thrombus to heal the wound in the plaque. However, the thrombus can grow in size, causing plaque to clog blood vessels more severely.[12–14]

Acute myocardial infarction (AMI) results from a sudden blockage of one or more epicardial coronary arteries for more than 20 to 40 minutes. The occlusion is usually thrombotic and occurs as a result of rupture or erosion of the atherosclerotic plaque in the coronary artery, thereby the myocardium to be deprived of oxygen. This condition results in disruption of the sarcolemma and relaxation of myofibrils, followed by mitochondrial change.[15] Ischemia for an extended period of time results in liquefactive necrosis of the myocardium. Necrosis progresses in a predictable pattern, starting from the subendocardial layer, and then progressing to the subepicardial layer. The location of the infarct determines whether or not cardiac function is impaired as a result of this process. This infarcted area then heals and undergoes remodeling, which is characterized by scar tissue formation, dilatation, segmental hypertrophy of the remaining tissue, and cardiac dysfunction.[16]

Cardiosphere-Derived Cells (CDC)

Various new therapeutic strategies have been developed in an effort to repair damaged cardiac myocardium after myocardial infarction, including the use of stem cell transplantation.[17] Types of stem cell modalities that have the potential to be used in cardiac cell therapy are bone marrow-derived stem cells (BMC), and adipose-derived stem cells. cells (ADSC), mesenchymal stem cells (MSC), and cardiosphere-derived cells (CDC).[6,18] Various studies that have been conducted previously indicate that CDC is a cardiac cell therapy agent that has a higher efficacy level than BMC and ADSC in increasing cardiac function, improvement of cardiac morphology, cell engraftment, myogenic differentiation, and reduction of apoptotic cells.[19] On the other hand, a comparative study between the CDC and MSCs conducted by Walravens et al. found that the CDC had a better capacity to reduce wound size due to myocardial infarction.[20]

CDC is a cell that has a high rate of proliferation rate and is derived from cultured percutaneous endomyocardial tissue biopsy samples.[8] In addition, CDC has also been isolated from cadaveric myocardium and canine heart organs.[21,22] CDC meet the criteria as a stem cell modality because it is clonogenic and has multilineage potential.[23] Specifically, CDC belongs to a heterogeneous population of stem cells because it expresses the TGF-β subunit (CD105), c-kit, markers of MSCs (CD90 and CD73), hematopoietic markers (CD45, CD34, and CD133), and markers of endothelial cells (CD31 and CD34).[8] Several studies have shown that CDC plays a role in the regeneration of cardiac organs that have decreased function due to disease/abnormalities (Table 1).

However, direct administration to the infarcted area would result in the CDC having low cell retention and poor cell engraftment mechanism. This is caused by cellular apoptosis events induced by an ischemic local environment and the presence of physical pressure from the contracting heart.[27] The low retention of CDC will have implications for decreasing the efficiency of the therapy given so it is necessary to increase retention to maximize the potential of modalities such as cardiac cell therapy. In response to this problem, Selvakumar et al. used hydrogel encapsulation as a carrier for stem cells to optimize their performance as therapy. In addition,

Table 2. Clinical Trial of CDC Efficacy.

Clinical Trials and Stages	Method of Application	Dosage of CDCs	Duration of Measurement	Adverse Effect	Author, Year
Intracoronary Cardiosphere-Derived Cells after Myocardial Infarction: Evidence for Therapeutic Regeneration in the Final 1-Year Results of the CADUCEUS (CArdiosphere-derived aUtologous stem Cells to Reverse Ventricular Dysfunction) Trial	Clinical Trial Phase I (NCT00893360)	A prospective, randomized, dose escalation study with CDC administration via post-AMI arterial infusion using autologous stem cells from endomyocardial biopsy.	31 post-AMI participants with moderate left ventricular dysfunction (Ejection fraction 25 to 45%) due to coronary artery atherosclerotic disease. (23 participants in the CDCs group and 8 participants in the control group)	Significant reduction in scar tissue increased viability of myocardium and improvement of regional contractility.	Malliaras et al, 2014[50]
Safety and Efficacy of Intracoronary Infusion of Allogeneic Human Cardiac Stem Cells in Patients With ST-Segment Elevation Myocardial Infarction and Left Ventricular Dysfunction: A Multicenter Randomized, Double-Blind, and Placebo-Controlled Clinical Trial	Clinical Trial Phase I/II (NCT02439398)	A randomized double-blind placebo-controlled study with a suspension of allogeneic cardiac stem cells (CSC) administration via intracoronary infusion in the acute phase of first AMI.	49 post-AMI participants with left ventricular dysfunction (ejection fraction ≤45%), infarct size ≥25% of left ventricular mass, and high risk of developing chronic heart failure	No significant differences in infarct size reduction by -2,3% (95% CI, −6.5% to 1.9%), indices of left ventricle remodeling, laboratory assessments, functional class, quality of life scores, and immunologic events.	Aviles et al, 2018[51]
Administration of Cardiac Stem Cells in Patients with Ischemic Cardiomyopathy (the SCIPIO Trial): Surgical Aspects and Interim Analysis of Myocardial Function and Viability by Magnetic Resonance	Clinical Trial Phase I (NCT00474461)	A randomized study with administration of CSC via intravenous infusion post-AMI	33 participants with heart failure (HF) with an LVEF ≤ 40%, evidence of a previous myocardial infarction (MI), and need for coronary artery bypass graft surgery (CABG)	Increased cardiomyocyte levels, reduced scarring of the infark, and significantly improved left ventricular function	Chugh et al, 2012[52]
Intracoronary ALLogeneic heart STem cells to Achieve Myocardial Regeneration (ALLSTAR): a randomized, placebo-controlled, double-blinded trial	Clinical Trial Phase II (NCT01458405	Randomized study placebo-controlled with CDC administration via intracoronary infusion	142 post-AMI participants with left ventricular (LV) ejection fraction <45% and LV scar size ≥15%	Improves segmental myocardial function especially segmental myocardial circumferential strain (Ecc) in segments containing scars post-AMI.	Makkar et al, 2020 and Ostonoveh et al, 2021[53,54]

Table 3. ClinClinical Trial of CDC Safety.

Study	Stages of Clinical Trial	Methodology of the Study	Number of Participants	Efficacy (Study Outcome)
Intracoronary Cardiosphere-Derived Cells after Myocardial Infarction: Evidence for Therapeutic Regeneration in the Final 1-Year Results of the CADUCEUS (CArdiosphere-derived aUtologous stem Cells to Reverse Ventricular Dysfunction) Trial	Intracoronary infusion 1.5-3 months post MI	First group: 12.5 x 106 autologous cells Second group: 25 x 106 autologous cells Third group (control): usual medical management	6-12 months	No serious adverse effect (SAE) related to the biopsy with the only SAE related to the study is a non-ST segment elevation MI (NSTEMI) in 1 patient of the CDC group occurring 7 months post-infusion. No other event including death, major adverse cardiac events (composite of death and hospital admission for heart failure or nonfatal recurrent MI), or tumor formation seen on MRI.
Safety and Efficacy of Intracoronary Infusion of Allogeneic Human Cardiac Stem Cells in Patients With ST-Segment Elevation Myocardial Infarction and Left Ventricular Dysfunction: A Multicenter Randomized, Double-Blind, and Placebo-Controlled Clinical Trial	Intracoronary infusion with 2-phase including open dose-escalation phase and double-blind randomized phase.	Escalation-dose phase: 10 × 106 allogeneic CSCs, 20 × 106 allogeneic CSCs, and 35 × 106 allogeneic CSCs Double-blind randomized phase: 35 × 106 allogeneic CSCs	8 months	No adverse effects linked to CSC administration in 12 months post-treatment including ischemia, anaphylaxis, hemodynamic instability, or ventricular arrhythmias, deaths, or major adverse cardiac events-MACE (all-cause death, reinfarction, hospitalization because of HF, sustained ventricular tachycardia, ventricular fibrillation, and stroke)
Administration of Cardiac Stem Cells in Patients with Ischemic Cardiomyopathy (the SCIPIO Trial): Surgical Aspects and Interim Analysis of Myocardial Function and Viability by Magnetic Resonance	Intracoronary injection of cardiac stem cells through expanded autologous c-kit positive cardiac stem cells.	Infarct region: Anterior Left Ventricle Wall: 1 × 106 CSCs were injected into the graft supplying the left anterior descending artery Other regions: 5 × 105 CSCs were injected into the graft(s) supplying those regions	4 months	Minimal complications such as left internal mammary artery (LIMA) dissection repaired with covered stent and elevated cardiac enzymes after balloon inflation consistent with peri-procedural MI appears in this research.
ALLogeneic Heart Stem Cells to Achieve Myocardial Regeneration (ALLSTAR Trial) (Clinical Trial Phase II)	Intracoronary infusion into the infarct-related artery using stop-flow technique. The infusion included three cycles: 2.15 mins of balloon inflation, 15 s of wash, 1.45 mins of cell infusion, and followed by 15 s of wash	25 million of CAP-1002 Allogeneic Cardiosphere-Derived Cells	6- and 12-months post-infusion	No adverse events led to early removal of any patient from the study; however, two serious events were linked to the intracoronary infusion procedure: acute myocardial infarction and femoral artery pseudoaneurysm.

the study conducted by Li et al. explained that the retention of stem cells in an environment with high reactive oxygen species (ROS) levels can be increased by using hydrogel encapsulation.[29] Therefore, to optimize the function of the CDC in regenerating the heart, it is necessary to protect and maintain retention by using a hydrogel-mediated encapsulation method.

In addition, the research conducted by Ottersbach et al. implemented the use of superparamagnetic microspheres (SPM) to increase the localization capability of CDC to be able to demonstrate its effectiveness in global myocyte cell repair in patients with ischemic heart disease such as myocardial infarction.[30] Utilization of SPM is also able to increase retention of CDC so that it can survive blood flow and heart contractions, as well as improve the quality of therapeutic outcomes because it increases cell engraftment in the long-term use.

Collagen-Based Hydrogel

Hydrogel is a porous biomaterial with a three-dimensional structure that has a high hydration status and can encapsulate living cells.[27,31] The high hydration status of hydrogels can assist in facilitating the mechanism of exchange of nutrients and metabolic waste products, as well as providing a hydrated and immune-protected environment. for the encapsulated cells.[27] On the other hand, the soft nature, biodegradability, and high biocompatibility as well as the ownership of structures that resemble macromolecular components of the body support the use of hydrogels as an ideal therapeutic delivery medium.[32] There are two groups of hydrogels based on the type of base material used, namely natural hydrogels (natural hydrogels) and synthetic hydrogels (synthetic hydrogels).[27,31] Synthetic hydrogels are a group of hydrogels whose basic ingredients are in the form of modified natural biopolymers or artificial biopolymers. Meanwhile, natural hydrogel is a hydrogel group with basic ingredients derived from natural biopolymers. Some of the characteristics that can be found in natural hydrogels are that they can be biodegraded by cellular enzymes, good biocompatibility, and can maintain their biochemical and biological properties.[27,31] Most of the compositions of these natural biopolymers consist of protein and polysaccharides, thus enabling the water absorption process., nutrient exchange, and elimination of metabolic products.[31,33] Therefore, natural biopolymers can facilitate increased cell survivability and facilitate the motility of the cells they carry. Several types of hydrogels based on natural biopolymers have been used in several clinical applications as cell carriers for cardiac tissue repair therapy, one of which is collagen.

Collagen is a protein that is the main component of the extracellular matrix of the heart.[31] Collagen is composed of a combination of chains that are folded into a tight left-handed helix, where the chain has the characteristic of having an unbroken sequence consisting of the repetition of glycine-proline-hydroxyproline amino acid.[34] Within each of the three left-handed helices of collagen there will be right-handed folds.[34] Collagen can be obtained by implementing decellularization methods, preserving the original tissue structure, or using extraction methods.[31] The use of collagen as a hydrogel base material has also been studied extensively, in vivo and in vitro. Based on several studies that have been carried out, there are several benefits such as stimulating myocardial cytokine profile, angiogenesis, reducing fibrosis and preventing cell death, having a cardioprotective effect, increasing stem cell adhesion, and increasing the delivery of bioactive molecules for myocardial repair and regeneration.[35] In addition, collagen can also be degraded by the body with the help of the enzyme collagenase. Natural biopolymers such as collagen are pH-responsive in the acidic category so that they can be used as the basis of therapeutic agents with a target in the form of low-pH infarct tissue.

Up to this point, 28 types of collagens have been identified based on their polypeptide sequence.[34] One of the types of collagen found to have high levels in the heart is type I collagen (±85% of the total collagen).[36] Type I collagen can be used as a base material hydrogel because it has a high level of permeability and biocompatibility behavior. In addition, type I collagen can facilitate the transport of stem cells to the microenvironment to maintain cell survival and proliferation, as well as mediate the extension of cell retention.[37,38] The use of type I collagen-based hydrogels has also been applied clinically in experimental animals induced by myocardial infarction.[11]

However, there are some disadvantages of hydrogels based on natural biopolymers such as experiencing a rapid degradation process and having poor mechanical strength.[31,39] As an effort to slow down the degradation process of hydrogels mediated by matrix metalloproteinase (MMP)-type proteases, it can be done

by mixing doxycycline, which plays a role in an MMP inhibitor, in the hydrogel matrix.[40] On the other hand, the study conducted by Efraim et al. stated that the genipin cross-linking approach accompanied by a low dose of chitosan on the collagen-based hydrogel could be implemented to increase the mechanical strength of the hydrogel up to 36.8 kPa.[41]

CDC Extraction and Modification Procedure

The CDC extraction process is initiated by taking percutaneous endomyocardial tissue specimens, approximately 276 mg, from an individual with AMI within the last 30 days by the biopsy method.[8,24,42] To maintain tissue viability before processing, the biopsy specimens are stored on ice in a cardioplegic solution with a high potassium content.[43]

Processing of biopsy specimens begins with cutting the specimen into fragments with a size of <1 mm3, then the preparation is cleaned and given trypsin. The fragments as cardiac explants were then cultured on Petri dishes that had been coated with fibronectin and placed in cardiac explant media (CEM). After 3-4 days of exposure to 5% CO2 gas and a temperature of 37°C, there was a growth of a layer of explants with the characteristics of cells similar to the stroma. Cells that are loosely attached to the area around the explants (called cardiac outgrowth cells) are then isolated using an enzymatic process with trypsin. Cardiac outgrowth cells that have been successfully harvested will be cultured in Petri dishes coated with poly-D-lysine and placed in the cardiosphere growing media (CGM). Cardiosphere is estimated to be formed after 2-3 days and harvested. To obtain CDC, the harvested cardiosphere will be placed in an Erlenmeyer tube containing fibronectin and cultured at CEM.[24,43] The extracted CDC will be modified by implementing magnetic labeling using SPM. Based on the research by Ashur et al., SPM particles were utilized at CDC with the coincubation technique in culture for 24 hours.[8]

CDC Encapsulation Procedure with Collagen-Based Hydrogel

The procedure for making collagen-based hydrogel, especially type I collagen, is carried out by adding 1.1 ml of saline solution to 0.9 ml of type I collagen (derived from sterilized rat tails) in acetic acid.[11,44] This process will produce a liquid mixture. of 2 ml of collagen-saline and then the pH was adjusted to 7.4 using 0.1 M NaOH.[15] After the hydrogel was formed, modifications were made with the incorporation of an MMP inhibitor, namely doxycycline to slow down the biodegradation of the modality.[40] Furthermore, the addition of a reinforcing biomaterial in the form of genipin (0.1 gr/gr hydrogel) and chitosan (0.2 gr/gr hydrogel) was purposely to control the mechanical strength of the hydrogel.[41]

The hydrogel-based encapsulation method will be based on the methods proposed by Li et al. (2016).[29] The encapsulation procedure was initiated by thoroughly mixing the CDC suspension ratio of 0.5 ml and 1 ml of hydrogel solution at 4°C temperature. Then it was incubated at 37°C for 20-30 minutes to produce the CDC modality encapsulated by a collagen-based hydrogel.[29]

Method of Administration, Dosage, and Recipient Eligibility Criteria

The administration method of a therapeutic modality is an important consideration when discussing the most effective use of stem cell-based therapies for tissue repair after myocardial infarction. The aspects that need to be considered in determining the method of administration from the CDC are the risk of side effects, retention of stem cells, and the usefulness of therapy for patients.[8]

Administration of collagen-based hydrogel encapsulated CDC will be carried out using the intracoronary infusion method with continuous flow in the three main coronary arteries.[45] This method was chosen as the intracoronary approach can prevent the formation of CDC aggregation in vivo and can be carried out simultaneously when carrying out the percutaneous coronary intervention (PCI).[46] Research by Gallet et al. also stated that there were no side effects associated with the intracoronary administration of stem cells for post-AMI therapy.[47] In addition, this method is also useful in reducing the size of the infarct wound effectively, preventing adverse tissue reconstruction, and improving neovascularization and cardiac function.[47] Approaches to the disadvantages that can be encountered through the intracoronary infusion method such as low cell retention have also been carried out by encapsulating CDC using collagen-based hydrogel.

For many regenerative therapies, including those involving cardiac cells, precise timing and dosing are critical to enhance recovery and minimize further damage. Based on previously conducted trials, this stem cell-based therapy can be administered to patients with a myocardial infarction within 30 days up to the past 4 weeks post-AMI.[42] The dosage of CDC administered can be categorized into three distinct regimens: low dose (12.5 million cells), intermediate dose (17.3 million cells), and high dose (25 million cells). A safety review determined that a dose of 25 million cells is the maximum safe therapeutic amount. Furthermore, as proposed by previous studies, the recipients of this modality must meet several eligibility criteria: 1) must be over 18 years old; 2) have successfully undergone stent placement; 3) achieve a minimum Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 in the affected artery.[42]

Pharmacokinetics of Collagen-Based Hydrogel Encapsulated CDC

Administration of CDC with type I collagen-based hydrogel encapsulation via intracoronary injection showed good absorption by the body where CDC could work optimally with minimum cell retention. Along with the increased absorption, CDC can be well distributed in the myocardium which undergoing AMI as well. This can happen because type I collagen-based hydrogel mediates cell engraftment and is immunoprotective towards CDC so that CDC can survive in an inflamed environment due to the AMI itself.[29] Based on clinical trials regarding the effectiveness of CDC as a therapy in previous heart disease, no significant side effects were found. However, studies on the effectiveness of the CDC are still ongoing to review the long-term effects of CDC administration to reshape the myocardium after AMI.

The metabolism of CDC encapsulated by type I collagen-based hydrogel in the body is also slowed by the addition of doxycycline so that it isn't easily degraded and can work optimally in target areas of the myocardium experiencing AMI. Naturally, collagen-based hydrogel degrades after 5-6 weeks of administration.[48]

Pharmacodynamic of Collagen-Based Hydrogel Encapsulated CDC

In general, CDC-encapsulated type I collagen-based hydrogel with the addition of doxycycline reduces the risk of post-AMI scarring, increases myocardial viability, and improves myocardial function so that cardiac construction can be maintained. Intracoronary administration minimizes invasive effects on the body where the transport of CDC type I collagen-based hydrogel encapsulated via this intracoronary catheter can maintain coronary flow without disrupting the systolic and diastolic phases of the heart.[49]

Clinical Trial of CDC Efficacy and Safety Outcomes in Post-AMI

Several clinical trials related to the efficacy and safety of CDC as a modality in the treatment of AMI have shown promising results. Based on the preclinical trial of type I collagen-based hydrogel encapsulated CDC administration, it showed a cardioprotective effect that increased the level of cardiomyocytes after AMI. The following is a table of several clinical trials related to CDC administration as post-AMI therapy (Table 2. and 3.).

Conclusion

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality worldwide. Myocardial tissue damage following AMI increases the risk of recurrence, which current management strategies have not fully addressed. Stem-cell therapy utilizing type I collagen-based hydrogel encapsulated CDCs shows promise in advancing post-AMI management by promoting cardiomyocyte regeneration, thereby reducing the risk of recurrent AMI and improving both the functional and structural integrity of the heart. Moreover, safety data from existing trials have demonstrated no serious adverse effects, including the absence of MACE, arrhythmias, or mortality. This favorable safety profile underscores the potential of stem cell therapy as a viable and promising tissue repair agent, offering significant benefits without compromising patient safety.

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Conflict of Interest

There are no conflicts of interest.

List of Abbreviations

ACEi	Angiotensin-Converting Enzyme inhibitors
AMI	Acute myocardial infarction
CDC	Cardiosphere-Derived Cells
CEM	Cardiac Explant Media
CGM	Cardiosphere Growing Media
TIMI	Thrombolysis in Myocardial Infarction

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