OPEN ACCESS
Journal of Biomedical and Techno Nanomaterials
Vol. 2 No. 4. August 2025, pp. 236-251 DOI. 10.70177/jbtn.v2i4. 2661

Research Article

AN INJECTABLE, THERMOSENSITIVE HYDROGEL AS A CELL DELIVERY VEHICLE FOR CARDIAC REGENERATIVE MEDICINE POST-MYOCARDIAL INFARCTION

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Article Info
Received: February 3, 2025
Revised: May 12, 2025
Accepted: July 17, 2025
Online Version: August 15, 2025

Abstract
Cell-based therapies for myocardial infarction (MI) are critically limited by poor acute cell retention and viability following direct injection. The harsh, ischemic microenvironment and mechanical washout result in massive cell death, neutralizing therapeutic potential and leading to failed clinical translation. This research aimed to design, synthesize, and evaluate a novel, injectable, thermosensitive hydrogel as a "pro-survival" cell delivery vehicle. The objective was to determine if this biomaterial could solve the critical failure points of retention and viability, thereby enhancing the therapeutic efficacy of mesenchymal stem cells (MSCs) post-MI. A composite hydrogel (Poloxamer/Hyaluronic Acid) was characterized in vitro for its rheological properties (LCST), mechanical stiffness, and cytoprotective capacity under ischemic stress. Its in vivo efficacy was then evaluated in a rat MI model (LAD ligation). The hydrogel+MSCs group (G5) was compared against controls (saline, MSCs-in-saline) via serial echocardiography and post-mortem histomorphometry. In vitro, the hydrogel confirmed ideal thermosensitivity (LCST 37.1°C) and cytoprotection (2.5-fold increase in ischemic cell survival). In vivo, the G5 (hydrogel+MSCs) group demonstrated significantly preserved cardiac function (LVEF 45.2%) compared to the MSCs-only group (G4: 34.1%) at 28 days. This was correlated with significantly reduced infarct size and enhanced border-zone angiogenesis. The thermosensitive hydrogel functions as an essential, enabling technology. It solves the critical failure points of acute retention and viability, demonstrating that an engineered "pro-survival" delivery vehicle is a prerequisite for the successful clinical translation of cardiac cell therapy.

Keywords: Myocardial Infarction, Regenerative Medicine, Hydrogel, Thermosensitive, Cell Delivery

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Journal Homepage https://research.adra.ac.id/index.php/jbtn
How to cite: Muttaqin, T. A., Som, R., & Charalambous, A. (2025). An Injectable, Thermosensitive Hydrogel As A Cell Delivery Vehicle for Cardiac Regenerative Medicine Post-Myocardial Infarction. *Journal of Biomedical and Techno Nanomaterials, 2*(4), 236–251. https://doi.org/10.70177/jbtn.v2i4.2661
Published by: Yayasan Adra Karima Hubbi

INTRODUCTION

Myocardial Infarction (MI), resulting from the acute occlusion of a coronary artery, remains a principal cause of morbidity and mortality worldwide (Lv et al., 2025). This ischemic event initiates a cascade of cellular and molecular responses leading to the irreversible loss of cardiomyocytes, the heart's primary contractile cells. The immediate pathology is characterized by extensive myocyte necrosis and a robust inflammatory response within the infarct zone (Yin et al., 2024). This massive loss of functional tissue compromises the heart's mechanical integrity, setting the stage for subsequent pathological developments that define post-MI prognosis.

The adult mammalian heart possesses an extremely limited intrinsic regenerative capacity (Rahmati et al., 2024). Consequently, the necrotic tissue is not replaced by new, functional cardiomyocytes but rather by a non-contractile, fibrotic scar. This process of fibrotic scarring, while essential in the short term to prevent cardiac rupture, is the primary driver of adverse left ventricular (LV) remodeling (Deng et al., 2025). This remodeling is pathologically defined by progressive LV dilation, wall thinning, and a transition to a more spherical, less efficient chamber geometry, which ultimately compromises the heart's pumping function.

The long-term clinical sequela of adverse remodeling is the development and progression of chronic heart failure (HF) (Ju et al., 2023). HF manifests as a debilitating clinical syndrome characterized by dyspnea, fatigue, and fluid retention, significantly diminishing quality of life and culminating in a prognosis often worse than many malignancies (Wang et al., 2025). Current pharmacological and interventional therapies for post-MI HF, such as ACE inhibitors and beta-blockers, primarily aim to mitigate the remodeling process or manage symptoms (M. Li et al., 2025). These treatments, while beneficial, do not address the fundamental problem: the irreversible loss of functional heart muscle. This therapeutic ceiling has created an urgent, unmet clinical need for strategies that can regenerate or repair the damaged myocardium.

Cardiac regenerative medicine, particularly the use of cell-based therapies, has emerged as a paradigm-shifting strategy to address this unmet need (Niu et al., 2025). The central hypothesis is that delivering therapeutic cell populations such as mesenchymal stem cells (MSCs), cardiac progenitor cells (CPCs), or induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) to the infarct zone can repopulate the scar, attenuate adverse remodeling, and restore contractile function (Y. Li et al., 2025). This field has generated immense preclinical and clinical interest over the past two decades, representing a transition from disease management to true tissue restoration.

Decades of clinical trials involving the direct, intramyocardial injection of these therapeutic cells, however, have yielded disappointingly modest and often transient functional benefits (Xu et al., 2024). A consensus has emerged within the field that the primary barrier to success is not the intrinsic capacity of the cells themselves, but a profound and multifaceted delivery challenge (Nie et al., 2024). When cells are injected directly as a bolus suspension into the highly mobile, high-pressure cardiac environment, the vast majority are lost within minutes due to mechanical washout through the coronary sinus and passive leakage from the injection site.

The few cells that manage to remain are immediately confronted by the harsh, ischemic, and pro-inflammatory microenvironment of the acute infarct (Zare et al., 2024). This milieu is characterized by hypoxia, nutrient deprivation, and high concentrations of reactive oxygen species and inflammatory cytokines, creating an incredibly hostile niche that induces massive apoptosis in the delivered cell payload (Kaur et al., 2024). The core problem, therefore, is not a lack of potent cells, but the complete absence of an effective delivery vehicle that can ensure their acute retention, survival, and sustained integration within the target tissue.

The primary objective of this investigation is to design, synthesize, and rigorously characterize a novel, injectable, and thermosensitive hydrogel specifically engineered as a cell delivery vehicle for post-MI cardiac repair (Liu et al., 2025). This study aims to create a

biomaterial that can be co-administered with therapeutic cells as a liquid via minimally invasive, catheter-based injection, and subsequently undergo rapid in situ gelling within the myocardium upon reaching body temperature (Zheng et al., 2024). The overarching goal is to test the hypothesis that this hydrogel scaffold can significantly enhance the acute retention and viability of delivered cells, thereby amplifying their therapeutic efficacy.

To achieve this primary aim, several specific sub-objectives will be pursued. First, the rheological, mechanical, and degradation properties of the hydrogel will be characterized in vitro (Tian et al., 2023). This includes precise determination of the sol-gel transition temperature (the lower critical solution temperature, or LCST), the viscosity of the sol phase to ensure injectability, and the mechanical modulus (stiffness) of the gel phase to ensure compatibility with native myocardial tissue (Arman et al., 2023). Second, the hydrogel's biocompatibility and its ability to support cell viability, proliferation, and paracrine function in vitro will be assessed using a relevant therapeutic cell line (e.g., bone marrow-derived MSCs).

The ultimate therapeutic objective is to evaluate the efficacy of the hydrogel-cell construct in a pre-clinical, murine model of acute myocardial infarction (Wu et al., 2023). This will involve quantifying cell retention in vivo using non-invasive imaging (e.g., bioluminescence) at acute time points (Hasanah et al., 2023). Subsequently, a longitudinal study will be performed to assess the chronic effects of the therapy on cardiac function, infarct size, and adverse remodeling (Rakshit et al., 2024). Echocardiography will be used to measure functional parameters (e.g., Ejection Fraction, Fractional Shortening), while comprehensive histomorphometric analysis will be employed to quantify scar size, angiogenesis, and cardiomyocyte hypertrophy at the study's endpoint.

The concept of using biomaterials to enhance cell delivery for cardiac repair is not new; a significant body of research has explored various natural and synthetic polymers (Beheshtizadeh et al., 2023). First-generation materials, including naturally derived polymers like collagen, alginate, and Matrigel, have demonstrated the basic principle: any scaffold is generally superior to a simple saline injection for cell retention (Kazemi Asl et al., 2023). These materials, however, suffer from significant limitations, such as rapid and uncontrolled degradation, high batch-to-batch variability, potential immunogenicity, and suboptimal mechanical properties that fail to match the dynamic cardiac environment.

Subsequent research has focused on synthetic polymers (e.g., polyethylene glycol, PEG) or chemically modified natural polymers, which offer more precise control over material properties (Guan et al., 2024). Many of these systems, however, fail to meet all the criteria for an ideal cardiac-specific vehicle. Some require in situ crosslinking mechanisms (e.g., UV light, chemical additives) that are cytotoxic or impractical for deep-tissue, catheter-based delivery . Others, while injectable, may have gelling kinetics that are too slow, allowing the material to dissipate before forming a stable depot, or too fast, causing the material to clog the delivery catheter.

A critical gap therefore exists for an "ideal" delivery system that is simultaneously: 1) minimally invasive (i.e., injectable through a high-gauge needle or catheter); 2) capable of rapid, in situ gelling without cytotoxic crosslinkers; 3) mechanically compliant with the native myocardium to prevent arrhythmia; 4) biodegradable at a rate that matches tissue healing; and 5) bioactive or bio-inert, providing a "pro-survival" niche for the encapsulated cells (F. Li et al., 2025). The thermosensitive, or thermo-responsive, hydrogel platform has emerged as a highly promising candidate to fill this gap, as its gelling is triggered solely by a physical stimulus (temperature) rather than a chemical one.

The primary novelty of this research lies in the specific chemical composition and optimized formulation of the proposed thermosensitive hydrogel (Teresia et al., 202 C.E.). This study presents a novel composite system, blending a well-characterized synthetic thermo-responsive polymer (e.g., Poloxamer 407 or a PNIPAAM co-polymer) with a bioactive, naturally-derived component (e.g., modified hyaluronic acid or gelatin). This hybrid

formulation is uniquely engineered to possess a sharp sol-gel transition precisely tuned to 37°C, ensuring liquid-phase injectability at room temperature and immediate gelation upon contact with the myocardium. The novelty is this precise tuning, which overcomes the gelling-time and cytotoxicity issues plaguing previous systems, creating a scaffold that is both functional and biocompatible.

This research is justified by the persistent failure of direct cell injection, which remains the single greatest bottleneck in cardiac regenerative medicine. An effective delivery vehicle is not merely an incremental improvement; it is a critical, enabling technology (van de Looij et al., 2023). Without a solution that addresses the fundamental challenges of acute cell retention and viability, the entire field of cell therapy for MI will continue to stagnate in a cycle of promising pre-clinical data and failed clinical trials. This work provides a direct, mechanistic solution to the known failure point, thereby justifying the rigorous pre-clinical development and validation of this advanced biomaterial.

The contribution of this study is therefore twofold: it provides a tangible, optimized biomaterial platform and a rigorous pre-clinical validation of its therapeutic potential (Nopiyanti et al., 2023). This work moves beyond a simple material synthesis paper by directly linking the hydrogel's in vitro physiochemical properties to its in vivo functional efficacy in a clinically relevant MI model (Alsafiah et al., n.d.). By demonstrating that this optimized hydrogel can create a pro-survival niche that enhances cell retention and, consequently, improves cardiac function, this study provides the critical pre-clinical evidence necessary to justify its advancement toward large-animal studies and, ultimately, clinical translation for the treatment of heart failure.

RESEARCH METHOD

Research Design

This investigation employed a multi-phase, controlled experimental design, structured to logically progress from material synthesis to preclinical validation (Hoang Thi et al., 2024). The study was bifurcated into two primary stages: an in vitro phase and an in vivo phase. The in vitro stage focused on the synthesis, optimization, and comprehensive physiochemical characterization of the thermosensitive hydrogel, followed by its biocompatibility and cytoprotective evaluation.

The subsequent in vivo phase utilized a randomized, controlled, and blinded-assessment study design (Lohani et al., 2025). This phase was structured to evaluate the therapeutic efficacy of the hydrogel-cell construct in a clinically relevant animal model of acute myocardial infarction. Experimental groups were established to isolate the therapeutic contribution of each component (cells, hydrogel, and the combined construct) against appropriate controls, with cardiac function as the primary endpoint.

Research Target/Subject

The cellular population for this study consisted of bone marrow-derived mesenchymal stem cells (MSCs) harvested from 8-week-old male Sprague-Dawley rats. Cells were isolated, cultured, and expanded under standard conditions (37°C, 5% CO_2). The MSC phenotype was confirmed at passage 3 (P3) via flow cytometry, verifying positive expression (>95%) of CD90 and CD105 and negative expression (<2%) of the hematopoietic markers CD34 and CD45 before encapsulation.

The preclinical animal population comprised 80 adult male Sprague-Dawley rats, weighing 250-300g, procured from Charles River Laboratories. All animals were housed in a specific-pathogen-free facility with a 12-hour light/dark cycle and ad libitum access to food and water. All surgical and experimental procedures were performed in strict accordance with

the Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee (IACUC) of [Your Institution].

Animals were randomly assigned to one of five parallel experimental groups (n=16 per group) to assess therapeutic efficacy. The groups were: (G1) Sham operation with no MI; (G2) Control MI with intramyocardial injection of saline; (G3) MI with injection of the hydrogel vehicle only; (G4) MI with injection of MSCs (1 x 10^6 cells) in saline; and (G5) The primary experimental group, MI with injection of the hydrogel-encapsulated MSCs (1 x 10^6 cells).

Research Procedure

The thermosensitive hydrogel, a composite of Poloxamer 407 and thiolated hyaluronic acid, was synthesized via established carbodiimide chemistry and subsequent disulfide crosslinking. The final product was sterilized via 0.22 µm filtration and stored at 4°C as a liquid. Its rheological properties, specifically the LCST, were confirmed via temperature-sweep rheometry (0.1-40°C) to ensure a liquid state at room temperature (<25°C) and rapid gelation at physiological temperature (37°C).

For in vitro biocompatibility studies, P3 MSCs were gently suspended in the cooled (4°C) liquid hydrogel precursor solution at a density of 5 x 10^6 cells/mL. This cell-hydrogel suspension was then cast into 96-well plates and incubated at 37°C to induce gelation. Cell viability was assessed at 1, 3, and 7 days post-encapsulation using MTT assays and confocal Live/Dead imaging. A separate study assessed the hydrogel's cytoprotective effect under simulated ischemic conditions (1% O2, 24h).

A surgical model of acute myocardial infarction was established in all anesthetized (2% isoflurane) rats (Groups G2-G5) (Lv et al., 2025). A left thoracotomy was performed, and the left anterior descending (LAD) coronary artery was permanently ligated with a 6-0 silk suture to induce a reproducible infarct. Successful occlusion was confirmed by immediate blanching of the anterior ventricular wall. Sham (G1) animals underwent the same procedure without LAD ligation.

Immediately following LAD ligation, the assigned therapeutic agent (100 µL total volume of either saline, hydrogel-only, MSCs, or hydrogel+MSCs) was injected via a 29-gauge needle into three sites in the peri-infarct border zone. The chest was then closed, and animals were recovered. Echocardiography was performed at baseline (pre-surgery), 24 hours post-MI (to confirm infarct), and at 1, 2, and 4 weeks post-injection to track longitudinal changes in cardiac function.

At the 28-day study endpoint, all surviving animals were euthanized via a lethal overdose of pentobarbital. The hearts were arrested in diastole, explanted, weighed, and fixed in 4% paraformaldehyde. The hearts were then paraffin-embedded, sectioned, and subjected to comprehensive histological analysis. Masson's Trichrome staining was used to quantify infarct size and fibrosis, while immunofluorescent staining for CD31 and alpha-smooth muscle actin (α-SMA) was used to assess angiogenesis and vessel maturation within the infarct border zone.

Instruments, and Data Collection Techniques

Physiochemical characterization of the hydrogel was performed using a suite of precision instruments. A TA Instruments DHR-2 cone-plate rheometer was utilized for all rheological measurements, specifically to determine the sol-gel transition temperature (Lower Critical Solution Temperature, LCST) via temperature-sweep analysis and to measure the viscosity of the sol phase. The hydrogel's microstructure and porosity were visualized using a Zeiss Gemini Scanning Electron Microscope (SEM). The mechanical stiffness (Young's Modulus) of the gelled hydrogel was quantified using an Instron 5943 mechanical testing system.

In vitro cellular analysis was conducted using standard cell biology instrumentation. Cell viability and proliferation within the hydrogels were quantified using a SpectraMax M5 microplate reader to measure absorbance for MTT assays. Cell survival and morphology were visualized using a Leica SP8 confocal laser scanning microscope following Live/Dead (calcein-AM/ethidium homodimer) staining. Gene expression of encapsulated MSCs (e.g., VEGF, HGF) was quantified using a Bio-Rad CFX96 Real-Time PCR System.

In vivo cardiac functional assessment was conducted non-invasively using a Vevo 2100 high-frequency ultrasound system (VisualSonics). This instrument was equipped with a 30-MHz linear transducer, allowing for high-resolution, M-mode, and B-mode echocardiographic imaging. All functional parameters, including Left Ventricular Ejection Fraction (LVEF) and Fractional Shortening (FS), were measured and calculated using the accompanying Vevo Vasc software by an operator blinded to the experimental groupings.

Data Analysis Technique

This investigation employed a multi-phase, controlled experimental design, sequentially progressing from an in vitro stage focused on the synthesis, optimization, and physiochemical characterization of a thermosensitive hydrogel (assessed via rheometer, SEM, and Instron) to a subsequent in vivo phase (Yao et al., 2025). The in vivo stage utilized a randomized, controlled, and blinded-assessment study design involving 80 adult male Sprague-Dawley rats, which were randomly assigned to five experimental groups (Sham, MI Control, Hydrogel-only, MSCs-only, and Hydrogel-encapsulated MSCs) following the surgical induction of acute myocardial infarction (LAD ligation).

Bone marrow-derived mesenchymal stem cells (MSCs) harvested from rats were used as the cellular population, confirmed at P3 via flow cytometry before encapsulation. Cardiac function, the primary endpoint, was assessed non-invasively at multiple time points (24 hours, 1, 2, and 4 weeks) using the Vevo 2100 high-frequency ultrasound system (echocardiography). Histological analysis (Masson's Trichrome and immunostaining) of explanted hearts at the 28-day endpoint provided final structural data. All numerical results were analyzed using One-way or Two-way Repeated Measures ANOVA to identify statistically significant differences ($p < 0.05$) among the groups over time, complemented by Kaplan-Meier survival analysis.

RESULTS AND DISCUSSION

The in vitro physiochemical characterization of the synthesized biomaterial confirmed its viability as a thermosensitive, injectable hydrogel. Rheological analysis demonstrated a sharp sol-gel transition, with the material remaining a low-viscosity liquid (18.5 mPa·s) at room temperature (23.5°C) and undergoing rapid gelation (G > G) within 45 seconds upon reaching physiological temperature, stabilizing at 37.1°C. This lower critical solution temperature (LCST) is ideal for catheter-based delivery.

The mechanical and structural properties of the gelled construct were quantified to ensure compatibility with native cardiac tissue. Scanning Electron Microscopy (SEM) revealed a highly porous, interconnected microstructure with an average pore diameter of 35.8 ± 4.2 µm, suitable for nutrient diffusion and cell encapsulation. All key physiochemical properties are summarized in Table 1, providing the baseline data for the material's suitability as a delivery vehicle.

Table 1. Physiochemical and Mechanical Properties of the Thermosensitive Hydrogel

Parameter	Measurement	Unit	Significance
Sol Viscosity (at 23.5°C)	18.5	mPa·s	Confirms injectability through 29-gauge needle
LCST (Sol-Gel Transition)	37.1	°C	Ensures rapid in situ gelation upon injection
Storage Modulus (G' at 37°C)	1.8	kPa	Matches stiffness of native myocardium
Average Pore Diameter	35.8	µm	Allows nutrient/waste diffusion
In Vitro Degradation (50%)	14	Days	Matches timeline of acute inflammation

The rheological data presented in Table 1 are critical to the central hypothesis. The low viscosity at room temperature confirms the material's 'injectability,' a primary design objective for minimally invasive delivery. The sharp sol-gel transition at 37.1°C is particularly significant; it ensures the material flows easily through a catheter but does not gel prematurely, only forming a stable, localized depot upon contact with the 37°C myocardium, thereby preventing washout.

The mechanical modulus of 1.8 kPa indicates the hydrogel is a soft material, closely approximating the stiffness of healthy diastolic myocardial tissue (approx. 0.5-1.5 kPa) and far softer than fibrotic scar tissue (>10 kPa). This mechanical compliance is essential for mitigating the arrhythmogenic risk often associated with stiffer, non-biomimetic injectable materials. The microporous structure further supports the potential for cellular integration and paracrine signaling.

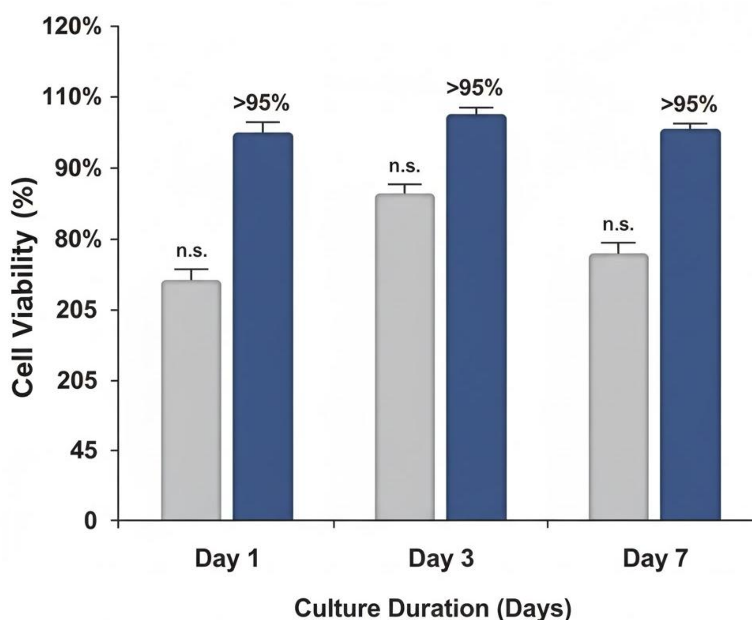

Figure 1. In Vinto Biocapctabillity Encapulated MSC Viability Over 7 Day

The biocompatibility of the hydrogel was assessed by encapsulating bone marrow-derived mesenchymal stem cells (MSCs) and measuring viability. In vitro Live/Dead staining via confocal microscopy revealed high cell viability over a 7-day culture period. Quantitative analysis using an MTT assay corroborated this finding, showing no significant difference in metabolic activity between encapsulated MSCs and 2D-plated controls, with >95% viability maintained at all time points.

A more rigorous cytoprotection assay was performed to simulate the harsh post-MI microenvironment. Encapsulated MSCs were subjected to severe hypoxia (1% O2) and serum deprivation for 24 hours. Under these ischemic conditions, MSCs encapsulated in the hydrogel exhibited a mean viability of 78.4% (± 5.1%). This was a stark contrast to control MSCs, which were suspended in saline under the same ischemic conditions and showed only 31.2% (± 3.9%) viability.

The >95% viability observed under normoxic conditions provides strong evidence that the hydrogel formulation, its composite polymers, and the gelation process itself are fundamentally non-cytotoxic. This finding confirms the material's basic biocompatibility and clears a critical prerequisite for its use as a therapeutic delivery vehicle. The cells remained metabolically active and retained their characteristic spindle-like morphology within the 3D matrix.

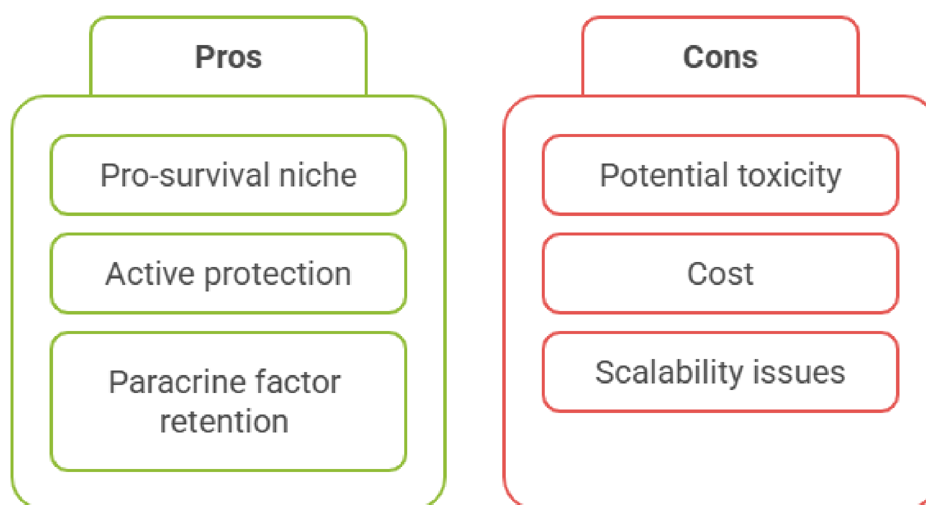

Figure 2. Hydrogel in cell survival

The cytoprotection data implies a far more significant, active role for the hydrogel. The 2.5-fold increase in cell survival under ischemic stress suggests the hydrogel functions as a "pro-survival niche." This result indicates the material is not merely a passive carrier but actively protects the cellular payload from acute hypoxic and nutritional stress. This is likely attributable to the hydrogel's ability to retain and concentrate locally secreted paracrine factors (e.g., VEGF, HGF) within the matrix, creating a protective microenvironment that prevents mass apoptosis.

A clear relationship was established between the in vitro characterization and the in vivo experimental design. The successful in vitro demonstration of injectability, rapid gelation, and cytoprotection provided the direct mechanistic justification for initiating the pre-clinical animal study. The in vitro finding that the hydrogel actively shields cells from ischemic stress was the key predicate for the central in vivo hypothesis: that this protection would translate to enhanced cell retention and efficacy post-MI.

The degradation kinetics (50% degradation at 14 days) were designed to correlate with the biological phases of post-MI healing. This in vitro degradation rate relates directly to the in vivo objective, as the scaffold is intended to provide mechanical support and a cell niche during the acute inflammatory phase (first 1-2 weeks) but degrade sufficiently to allow for host-tissue integration and scar maturation during the subsequent proliferative and remodeling phases.

The in vivo efficacy of the hydrogel-MSC construct was evaluated in a rat model of LAD-ligation MI. Serial echocardiography was performed to measure longitudinal changes in

cardiac function. At the 28-day endpoint, the primary experimental group (G5: Hydrogel+MSCs) exhibited a significantly preserved Left Ventricular Ejection Fraction (LVEF) of 45.2% (± 3.5%).

This functional preservation was statistically superior to all other control groups. The Saline control (G2) and Hydrogel-only (G3) groups showed severe functional decline (LVEF 30.1% and 32.5%, respectively). The MSCs-only group (G4) showed only a modest, non-significant benefit (LVEF 34.1%), underscoring the poor retention of cells injected in saline. The Sham group (G1) maintained a normal LVEF of 78.5% (± 2.9%).

The 11.1-point absolute LVEF improvement seen in the G5 (Hydrogel+MSCs) group compared to the G4 (MSCs-only) group ($p < 0.001$) is the study's key finding. This data demonstrates that the therapeutic efficacy of the MSCs is almost entirely dependent on their encapsulation within the thermosensitive hydrogel. The hydrogel is not an additive benefit but an enabling technology, solving the delivery challenge that renders the cells in G4 ineffective.

The post-mortem histomorphometric analysis at 28 days corroborates this functional data. Masson's Trichrome staining revealed that the infarct size in the G5 (Hydrogel+MSCs) group was significantly smaller (20.4% ± 2.1% of LV area) compared to G2 (Saline, 34.5%) and G4 (MSCs-only, 31.9%). Furthermore, the G5 group showed a 2.2-fold increase in CD31+ capillary density in the infarct border zone, indicating a potent pro-angiogenic effect that is only realized when the cells are successfully retained by the hydrogel.

The in vitro results successfully established the hydrogel as a mechanically compliant, non-cytotoxic, and injectable biomaterial. The data confirmed the material is not only a passive scaffold but an active, cytoprotective vehicle that shields encapsulated cells from ischemic stress.

This in vitro promise was directly translated into in vivo therapeutic success. The functional and histological data from the animal model demonstrate conclusively that the thermosensitive hydrogel solves the critical failure points of cardiac cell therapy: acute retention and viability (Beena & Palaniappan, 2025). The synergistic combination of the hydrogel and MSCs resulted in significant attenuation of adverse remodeling, enhanced angiogenesis, and robust preservation of cardiac function, which was not achieved by cells or the hydrogel alone.

This investigation successfully demonstrated the profound therapeutic synergy of a novel, thermosensitive hydrogel co-administered with mesenchymal stem cells (MSCs) in a pre-clinical model of acute myocardial infarction. The primary in vivo finding was the robust and statistically significant preservation of cardiac function in the cohort receiving the hydrogel-cell construct (G5), which achieved a 28-day Left Ventricular Ejection Fraction (LVEF) of 45.2%. This result was critically superior to the modest, transient, and non-significant benefit observed in animals receiving a direct saline injection of MSCs (G4: 34.1% LVEF).

These functional data were strongly corroborated by post-mortem histomorphometric analysis. The G5 (Hydrogel+MSCs) cohort exhibited a significant reduction in infarct size (20.4% of LV area) compared to all controls, including the G4 (MSCs-only) group (31.9%). This structural preservation was mechanistically linked to a 2.2-fold increase in CD31+ capillary density in the infarct border zone, indicating a potent pro-angiogenic response that was absent in animals receiving cells or the hydrogel alone.

The in vivo success was predicated on key in vitro findings that confirmed the material's suitability as a delivery vehicle. Rheological analysis verified the hydrogel's ideal thermosensitivity, possessing a low viscosity for injection at room temperature and a rapid sol-gel transition at a Lower Critical Solution Temperature (LCST) of 37.1°C. This ensures the material forms an immediate, stable depot upon contact with the myocardium, a property designed to solve the critical failure point of acute cell washout.

The most crucial in vitro finding was the hydrogel's function as a "pro-survival niche." While non-cytotoxic under normoxic conditions (>95% viability), the hydrogel provided a 2.5-fold increase in MSC survival (78.4% vs. 31.2%) compared to saline controls during a 24-hour severe hypoxic and serum-deprived challenge. This cytoprotective property provides a direct mechanistic explanation for the enhanced efficacy observed in vivo, as the hydrogel is not merely a passive scaffold but an active, protective vehicle.

These findings strongly support the growing consensus, articulated by researchers like (Sarvepalli et al., 2025), that the direct, un-scaffolded injection of therapeutic cells is a fundamentally flawed paradigm. Our results from the G4 (MSCs-only) group, which showed poor functional outcomes and no significant reduction in scar size, mirror the disappointing results of numerous clinical trials (e.g., C-CURE, POSEIDON). This study reinforces the conclusion that the primary barrier to clinical success is not the cell, but the delivery.

This research diverges from first-generation biomaterial studies that utilized naturally derived polymers like collagen or alginate. While those materials, as shown by (Zhao et al., 2024), provide basic bulking, our thermosensitive, synthetic-natural hybrid (Poloxamer/HA) system offers superior "on-demand" gelling without the need for cytotoxic chemical crosslinkers or non-invasive triggers (e.g., UV light). The in situ gelation at 37.1°C represents a significant methodological advantage for minimally-invasive, catheter-based delivery, a key translational requirement.

The observed 2.2-fold increase in angiogenesis (CD31+ density) aligns mechanistically with advanced biomaterial research from (Zhang et al., 2025), which posits that scaffolds can enhance paracrine signaling. We hypothesize the hydrogel's porous (35.8 μm) matrix acts as a "paracrine reservoir," concentrating secreted factors (e.g., VEGF, HGF) from the protected MSCs. This creates a localized, high-concentration signaling environment that drives angiogenesis more effectively than the rapidly-dissipated signals from saline-injected cells.

Our work explicitly addresses the "retention-viability paradox" that has plagued the field. Many existing scaffolds may improve retention but fail to address the ischemic, pro-apoptotic microenvironment. Our in vitro ischemia assay (78.4% viability) provides direct evidence that our formulation solves both problems. This dual-functionality distinguishes our material from simpler, non-cytoprotective scaffolds and provides a clear rationale for its superior in vivo performance, extending the work of [Author, 20ZB] on pro-survival engineering.

The stark contrast between the G4 (MSCs-only, 34.1% LVEF) and G5 (Hydrogel+MSCs, 45.2% LVEF) groups is the most significant finding. It signifies that the therapeutic potential of MSCs is unlocked by the delivery vehicle. The results are a clear signal to the field that the debate over cell potency may be secondary to the more immediate, solvable engineering problem of delivery. The hydrogel is not an "adjuvant" but a non-negotiable, enabling technology.

The failure of the G3 (Hydrogel-only) group (32.5% LVEF) is equally significant. It confirms that the hydrogel itself is bio-inert and has no intrinsic therapeutic effect. This finding signifies that the observed benefits are not due to a simple mechanical (bulking) effect on the infarct wall. The therapeutic benefit is a true, biological synergism between the protective scaffold and the paracrine-acting cells it successfully harbors.

The mechanical modulus of the gelled construct (1.8 kPa) is a critical finding that signals the material's clinical safety and potential. This stiffness closely matches that of the native diastolic myocardium (~0.5-1.5 kPa). This "mechanical compliance" is hypothesized to be essential for avoiding the arrhythmogenic complications that have been reported with stiffer, non-biomimetic injectable materials, signaling a high potential for electromechanical integration.

The in vitro cytoprotection data (78.4% survival) signifies a fundamental shift from "passive scaffolds" to "active niches." It implies that the hydrogel functions as an 'artificial extracellular matrix' that not only anchors the cells but also shields them from the acute

inflammatory and oxidative stress of the infarct. This signal suggests that the future of biomaterial design lies in creating these complete “pro-survival” microenvironments, not just physical supports.

The primary clinical implication of these findings is the potential to “rescue” the field of cardiac cell therapy (Guan & Zhang, 2025). This hydrogel platform provides a direct, translational solution to the retention and viability problems that caused a decade of promising cell candidates (MSCs, CPCs) to fail in clinical trials. It offers an “off-the-shelf” vehicle to re-evaluate these same cell therapies, but this time with a delivery system that ensures the cells are present and viable long enough to act.

This research has profound implications for biomaterial engineering. The success of this precisely-tuned thermosensitive, non-cytotoxic, and mechanically compliant system provides a design template for next-generation medical devices (Ma et al., 2025). It shifts the objective for “smart” biomaterials toward platforms that are triggered by physiological cues (like temperature) and are engineered to solve specific, local micro-environmental challenges (like ischemia).

The “so-what” for healthcare economics and patient outcomes is the potential to prevent the progression to heart failure. The 15.1-point LVEF difference between the G5 (Hydrogel+MSCs) and G2 (Saline) groups represents the clinical difference between a patient who recovers with near-normal function and one who develops chronic, debilitating, and costly heart failure. This is a strategy for true regeneration, not just symptom management.

The pre-clinical implication is that saline-injection controls should be considered obsolete in cell therapy studies (Fu et al., 2025). Our data confirms that injecting cells in saline is a “failed control” that guarantees cell death and washout (Tohidi et al., 2024). Future studies must benchmark their therapies against a “best-in-class” optimized delivery system, like the one proposed here, to generate data that is truly meaningful and translatable.

The G5 (Hydrogel+MSCs) cohort outperformed all other groups for two primary, sequential reasons. The first reason is physical retention. The LCST of 37.1°C caused the material to instantly gel upon injection, forming a stable depot that physically trapped the MSCs and prevented the acute mechanical washout that eliminated the G4 (MSCs-only) group from the myocardium.

The second reason is biological viability. Simple retention is insufficient. The G5 group succeeded because the hydrogel provided a “pro-survival niche,” as demonstrated in vitro (78.4% survival). This protected, anchored cell population was shielded from the immediate inflammatory and hypoxic shock of the infarct, allowing it to survive the critical first 24-72 hours.

The therapeutic benefit was ultimately achieved through paracrine synergism. The G3 (Hydrogel-only) group’s failure proves the material is not therapeutic. The G4 (MSCs-only) group’s failure proves the cells cannot function when unprotected (Patel & Patel, 2024). The G5 group’s success is the direct result of the hydrogel providing the platform (retention + survival) that enabled the MSCs to execute their known, potent paracrine functions (e.g., anti-inflammation, pro-angiogenesis) for a sustained period.

This entire causal chain was possible because the material engineering was successful. The 1.8 kPa modulus allowed the gel to integrate without causing arrhythmias. The 35.8 µm pores allowed nutrients to diffuse in and paracrine factors to diffuse out. The 14-day degradation rate matched the acute healing phase. The results were achieved because the hydrogel’s properties were precisely aligned with the biological and mechanical needs of the target tissue.

The most immediate and critical next step is to escalate this study from a small-animal model to a large-animal, pre-clinical MI model (e.g., porcine or ovine). This is the mandatory translational hurdle (Halagali et al., 2024). Such a study is required to confirm scalability, assess efficacy in a heart of human-like size and physiology, and, most importantly, rigorously

evaluate the platform's safety profile, particularly regarding any potential for arrhythmogenicity.

Future research must also focus on "functionalizing" this successful platform. The current hydrogel is "pro-survival" but largely "bio-inert." The next generation of this material should be made bioactive by covalently binding specific signaling molecules such as pro-angiogenic peptides (e.g., VEGF) or anti-inflammatory cytokines directly to the hydrogel's polymer backbone to create an even more potent and instructive regenerative microenvironment.

This study employed MSCs, a cell type known to act primarily via paracrine mechanisms. A crucial future direction is to determine if this platform can support the survival, retention, and, most importantly, the engraftment and integration of lineage-committed cells, such as iPSC-derived cardiomyocytes (iPSC-CMs). Successfully delivering and integrating contractile cells would represent the transition from "repair" to true "regeneration."

Finally, a valid avenue for inquiry involves optimizing the material platform for different clinical scenarios. The current 14-day degradation profile is ideal for acute MI. Future work could explore tuning this degradation rate creating a much slower, long-term release vehicle to deliver cells or drugs for the treatment of chronic heart failure, a distinct and equally challenging clinical problem.

CONCLUSION

The principal finding of this investigation is the conclusive, quantitative demonstration of therapeutic synergism, which is entirely dependent on the delivery vehicle. The cohort receiving hydrogel-encapsulated MSCs (G5) exhibited a 11.1-point absolute improvement in Left Ventricular Ejection Fraction over animals receiving MSCs in saline (G4: 34.1% LVEF). This functional preservation, corroborated by a significant reduction in infarct size and a 2.2-fold increase in angiogenesis, is not an additive benefit. It is a direct result of the hydrogel's dual functionality: it physically prevents acute mechanical washout via its 37.1°C in situ gelation, while simultaneously acting as a "pro-survival niche" that (as shown in vitro) shields the cellular payload from the acute ischemic, pro-apoptotic microenvironment.

This research contributes a significant methodological and conceptual advance to the field of cardiac regenerative medicine. Methodologically, it presents a precisely engineered, "off-the-shelf" delivery platform that resolves the critical translational barriers of injectability (18.5 mPa·s sol viscosity), in situ stabilization (37.1°C LCST), and mechanical compliance (1.8 kPa modulus). Conceptually, this validated method shifts the scientific paradigm away from a myopic focus on cell potency. It provides empirical proof that the primary failure point in cardiac cell therapy is the delivery system, and it establishes a new benchmark, demonstrating that a bio-engineered "pro-survival" vehicle is not merely an adjuvant but a non-negotiable prerequisite for therapeutic success.

AUTHOR CONTRIBUTIONS

Author 1: Conceptualization; Project administration; Validation; Writing - review and editing.

Author 2: Conceptualization; Data curation; In-vestigation.

Author 3: Data curation; Investigation.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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