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The Effect of Endogenous Stem Cell Mobilization on Congestive Heart Failure

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ABSTRACT

Heart failure (HF) is a significant cause of morbidity and mortality worldwide, with few reparative treatment options available. This preliminary trial investigated the potential of Endogenous Stem Cell Mobilization (ESCM), using a plant-based supplement documented to mobilize bone marrow stem cells (BMSCs), to enhance cardiac function in patients with heart failure. This plant-based supplement, Stemregen® Release, contains extracts of Aphanizomenon flos-aquae, sea buckthorn berry, Aloe macroclada, and Fucus vesiculosus. With a consumption of 2 capsules 3 times a day over six months, participants demonstrated substantial improvements in left ventricular ejection fraction (LVEF; 20.3%), reductions in natriuretic peptide (NP; 14.7%) levels, and enhanced quality of life as assessed by the Seattle Angina Questionnaire-7 (SAQ-7; 23.1%). ESCM using Stemregen® Release could be a non-invasive, safe, and effective strategy for improving heart failure outcomes, with broader implications for other degenerative conditions. Further studies are warranted to confirm the mechanisms of action and assess reproducibility in larger cohorts.

Keywords

Bone Marrow-derived Stem Cells, Endogenous Stem Cell Mobilization, Heart failure, Left Ventricular Ejection Fraction.

Introduction

Heart failure (HF) is a clinical syndrome characterized by the heart's inability to pump sufficient blood to meet the metabolic demands of the body, resulting in inadequate ventricular filling, reduced ejection of blood, or a combination of both. This condition manifests with symptoms such as fatigue, dyspnea, and peripheral edema and has become a global epidemic that significantly impacts life expectancy and quality of life.

Though relatively rare in individuals under 60 years of age [1], approximately 6 million Americans and 40 million adults worldwide have been diagnosed with HF. Projections indicate that the incidence of HF will increase by 46% by 2030, leading to more than 8 million affected adults in the United States and over 55 million globally. It is anticipated that one in five individuals in developed countries will develop HF during their lifetime [2]. Patients with HF also face a nearly tenfold higher risk of sudden cardiac death. Despite advancements in the treatment of heart disease, the prognosis for HF remains poor, with one-year and five-year mortality rates at 13% and 50%, respectively [3].

The primary etiologies contributing to the development of HF include chronic hypertension, often leading to left ventricular hypertrophy, coronary artery disease, and myocardial injury secondary to acute myocardial infarction (AMI) [4]. Despite significant advancements in the acute management of AMI, including the utilization of fibrinolysis, percutaneous coronary intervention, and other reperfusion therapies, approximately 30% to 40% of patients who experience an AMI will progress to develop HF within five years [5,6].

The conventional management of HF primarily focuses on palliative care, aimed at reducing blood pressure and enhancing hemodynamics through the administration of antithrombotic agents in conjunction with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers,

and aldosterone antagonists. These therapeutic strategies have been demonstrated to improve patient longevity [7]. However, these treatments are not reparative, and HF patients continue to experience a diminished quality of life and an elevated risk of sudden cardiac death.

Recent advancements in cellular therapies have introduced potential avenues for cardiac repair, with stem cell delivery emerging as a particularly promising strategy. These therapies involve the administration of stem cells either systemically or directly into cardiac tissue [8]. Notably, intramyocardial injection of adipose-derived stromal vascular fraction in patients with ischemic heart failure has been associated with a modest increase in maximum oxygen consumption during exercise treadmill testing [9].

In preclinical studies, intramyocardial injection of bone marrow-derived progenitor cells in mice improved cardiac function post-acute myocardial infarction (AMI) through mechanisms such as cellular cardiomyogenesis and neovascularization [10]. Benedek et al. conducted a controlled clinical trial involving 18 patients, nine of whom received intracoronary injections of autologous bone marrow-derived stem cells (BMSC). After a four-year follow-up, these patients exhibited slight improvements in ejection fraction (EF) and reductions in both the calcium score and the number of coronary plaques in segments treated with stem cells [11]. Similarly, in patients with ischemic heart disease, intracoronary injection of BMSC resulted in a significant reduction in infarct size, increased EF, and enhanced infarct wall movement velocity compared to controls [12]. These findings have been corroborated by additional studies, demonstrating consistent improvements in cardiac function following stem cell therapy [6,13-15].

Exogenously supplied stem cells have demonstrated the capacity to differentiate into endothelial cells and cardiomyocytes, a phenomenon first noted by Orlic et al. [16]. However, it is widely hypothesized that the paracrine effects of these transplanted stem cells play a pivotal role in cardiac repair, primarily through the recruitment of endogenous cardiac stem cells [17,18]. This hypothesis underscores the importance of the microenvironment in promoting cardiac regeneration, where the interaction between transplanted and resident cells drives the repair process.

Comparable findings have emerged from studies focusing on Endogenous Stem Cell Mobilization (ESCM). Under normal physiological conditions, BMSCs are continuously released into the peripheral circulation. However, their numbers escalate significantly in response to tissue or organ injury, a process mediated by the endogenous release of granulocyte-colony stimulating factor (G-CSF) from the damaged tissue [19,20]. The capacity to mobilize stem cells is increasingly recognized as a critical determinant of cardiovascular outcomes. Werner et al. [21] reported that patients with the highest mobilization of endothelial progenitor cells (EPCs) exhibited markedly lower 1-year cardiovascular mortality rates (1.8%) compared to those with the poorest mobilization (8.3%). The same phenomenon was reported by Sobrino et al. [22] after acute ischemic stroke.

Building on this natural response to injury, the potential of ESCM induced by G-CSF in cardiac repair has been explored. Orlic et al. conducted a study in which mice were injected with recombinant rat stem cell factor and recombinant human G-CSF for five days to mobilize stem cells, followed by the induction of AMI through coronary artery ligation [23]. The treatment continued with stem cell factor and G-CSF for up to 10 days. After 27 days, the treated mice exhibited a significant improvement in ejection fraction compared to controls, accompanied by the formation of new arterioles and capillaries. Other studies have corroborated these findings, reporting reduced left ventricular remodeling, ventricular hypertrophy, and cardiac remodeling [24-29].

In a porcine model of AMI, ESCM induced by erythropoietin and G-CSF was associated with significant increases in ejection fraction and improved diastolic function compared to the control group [30]. Similar outcomes have been observed in human studies, where G-CSF injection led to significant improvements in left ventricular ejection fraction and cardiac remodeling [31].

Despite the promising potential of G-CSF in stem cell mobilization and cardiac repair, the use of G-CSF has been associated with several adverse events that raise concerns about its safety. In a study involving six HF patients who received escalating doses of G-CSF, drug administration was discontinued in all participants due to elevated alkaline phosphatase levels [32]. Additionally, several clinical trials have been prematurely terminated due to complications such as excessive in-stent restenosis and acute coronary syndromes in patients with coronary artery disease [33-35]. Moreover, G-CSF has been reported to exert pro-inflammatory and thrombotic effects, which may negatively impact left ventricular recovery and increase the risk of stroke [36,37].

A meta-analysis that included more than 200 patients treated with G-CSF further highlighted these safety concerns, reporting four fatalities during the follow-up period, one case of spleen rupture, and three instances of subacute in-stent thrombosis or reinfarction [26,38]. Common side effects such as bone pain, myalgia, arthralgia, and headache, while typically not severe enough to necessitate discontinuation of treatment, are also frequently observed. More serious adverse effects, including interstitial pneumonitis, respiratory distress syndrome, thrombocytopenia, vasculitis, and notably aortitis, have been documented as well [39,40].

Given these safety issues, alternative approaches to stem cell mobilization that minimize adverse effects are of significant interest. Plant extracts that can be safely administered over extended periods have been reported to function as stem cell mobilizers. For example, extracts of *Aphanizomenon flos-aquae* [41], *Hippophae rhamnoides* [42], *Aloe macroclada* [43], *Fucus vesiculosus* [44,45], and *Panax notoginseng* [46] have all been documented to act as stem cell mobilizers. The use of these plant-based mobilizers has been associated with notable improvements in conditions such as HF, Parkinson's disease, stroke, spinal cord injury, and soft tissue injury [47-49]. This report presents

preliminary findings from a study investigating the effects of a blend of plant-based stem cell mobilizers on HF.

Methodology

Patients

A total of 10 patients were enrolled by Dr. Miguel Garber in his clinic setting. Inclusion criteria included patients between 40 and 80 years of age, with an ejection fraction (EF) below 45%, and a diagnosis with HF for over two years, classified as New York Heart Association (NYHA) class 2-3. Patients classified as New York Heart Association (NYHA) class 2 or 3 have moderate to severe heart failure: class 2 indicates mild symptoms with slight limitations during ordinary activity; class 3 indicates more significant limitations, with symptoms such as fatigue and shortness of breath occurring during less-than-ordinary activities. All participants were non-smokers and did not have any acute coronary or oncological disease, nor did they possess additional health risk factors.

Endogenous Stem Cell Mobilization (ESCM)

ESCM was induced by the daily intake of the supplement Stemregen® Release (Biomics LLC, dba Stemregen). Stemregen Release is a blend of plant extracts known to stimulate endogenous stem cell mobilization, comprising *Aphanizomenon flos-aquae extract* [41], *Hippophae rhamnoides* extract [42], *Aloe macroclada* extract [43], *Fucus vesiculosus* fucoidan [44,45], and *Panax notoginseng* extract [46,49]. Each dose of Stemregen Release (2 capsules) contained 1.43g of active ingredients. Participants were instructed to take two capsules three times daily. However, if adherence to this regimen was deemed challenging, participants were permitted to take three capsules twice daily. The participants consumed the product for six consecutive months and were assessed both before and after the supplementation period.

Participants Assessment

The parameters monitored throughout the study included the Seattle Angina Questionnaire-7 (SAQ-7), natriuretic peptides (NP), and left ventricular ejection fraction (LVEF), measured via echocardiography. Echocardiographic assessments were conducted using Simpson's method with the Esaote MyLab Gamma ultrasound system.

Statistical Analysis

All results are reported as mean ± standard deviation (SD) values. Student's t-test was applied to compare means. Correlation analyses between various parameters were conducted using Pearson correlation coefficients. For all statistical comparisons, a p-value of less than 0.05 was considered statistically significant.

Results

The study cohort consisted of 10 patients aged between 58 and 70 years (mean age 64.1 ± 3.65 years), 6 males and 4 females, who had been diagnosed with HF for a duration ranging from 24 to 41 months (mean duration 32.0 ± 6.8 months) as shown in Table 1. The initial LVEF of participants was between 40% and 45% (42.5 ± 1.6%). Natriuretic peptide (NP) levels ranged from 1770 to 2001 pg/mL (mean NP 1907.4 ± 78.6 pg/mL), and the Seattle Angina Questionnaire (SAQ) scores varied from 62 to 68 (mean SAQ 65.0 ± 2.1). Throughout the study, no participants reported any adverse events.

All participants were on established regimens that included various combinations of antihypertensive and antithrombotic drugs, along with statins, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs), diuretics, as well as beta-blockers and calcium channel blockers. No changes to participants' medication regimens were made prior to study initiation, and no modifications were recorded throughout the study period.

Left Ventricular Ejection Fraction (LVEF) Outcomes

Before ESCM supplementation (Figure 1 and Table 3), participants showed an average LVEF of 42.5 ± 1.6%, with individual values ranging from 40% to 45%. After six months of daily ESCM, LVEF increased by an average of 20.3 ± 3%, resulting in a post-intervention average of 51.1 ± 1.6%, with values ranging from 49% to 55%.

No significant correlation was observed between the magnitude of LVEF improvement and participants' age ($r = -0.007$) or time since diagnosis. However, there was a non-significant trend suggesting that participants with lower initial LVEF ($r = -0.15$) and those with a longer time since diagnosis ($r = 0.19$) tended to experience greater benefits from the intervention.

Natriuretic Peptides (NP)

After six months of daily ESCM supplementation (Figure 1 and Table 3), participants demonstrated an average decrease in natriuretic peptide (NP) levels by 14.7 ± 3%. The average NP level decreased from 1907.4 ± 78.6 pg/mL at the start of the trial to 1625.7 ± 8.6 pg/mL, indicating an improvement in cardiac function. The range of NP levels also shifted from 1770–2001 pg/mL at baseline to 1542–1773 pg/mL post-intervention. This reduction in NP levels reflects a positive response to the supplement, often used as a marker for heart failure severity.

Although there was a trend towards greater reductions in NP levels among younger participants ($r = 0.18$) and those with a more recent diagnosis ($r = 0.11$), as well as among participants with lower initial LVEF ($r = 0.16$) or higher initial NP levels ($r = 0.1$), these correlations did not achieve statistical significance.

Seattle Angina Questionnaire-7 (SAQ-7)

Before the trial began (Figure 1 and Table 3), participants had an average SAQ-7 score of 65.0 ± 2.1, with individual scores ranging from 62 to 68. After six months of daily ESCM supplementation, SAQ-7 scores improved by an average of 23.1 ± 6%, resulting in post-intervention scores ranging from 75 to 85. This notable improvement in SAQ-7 scores reflects enhanced angina-related health and quality of life following the ESCM intervention.

There was a tendency for greater improvements in SAQ-7 scores among older participants ($r = 0.18$) and those with lower baseline

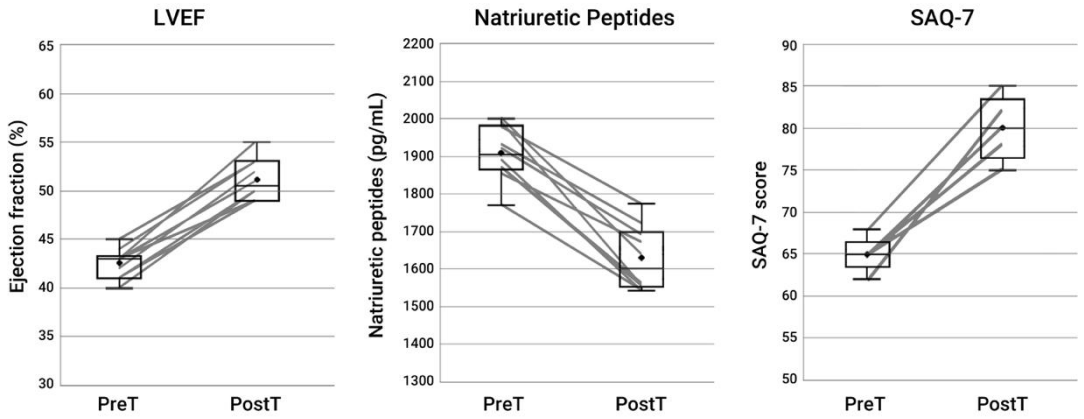

Figure 1: Left ventricular ejection fraction (LVEF), Natriuretic peptide (NP) levels, and Seattle Angina Questionnaire-7 (SAQ-7) scores before and after six months of ESCM supplementation.

SAQ-7 scores (r = 0.17), although no significant correlation was observed with the duration since diagnosis. A strong linear relationship (r = 0.9) was identified between SAQ-7 scores and LVEF, suggesting that the SAQ-7 score may serve as a reliable surrogate measure of LVEF.

Table 1: Patient Demographics (6 males, 4 females).

	Average	Range
Age (years)	64.1 ± 3.65	58 - 70
Duration with CHF (months)	32.0 ± 6.8	24 - 41

Table 2: Type of medical illness and baseline medications profile of patients.

Type of Medical Illness	**Percentage**
Hypertension	100%
Diabetes Mellitus Type 2	60%
Hypercholesterolemia	100%
Ischemic Heart Disease	100%
Prior Revascularization	40%
Type of Medication	**Percentage**
Statin	40%
Aspirin	100%
Beta-Blocker	100%
Calcium Channel Blocker	100%
Angiotensin Converting Enzyme Inhibitor (ACEI)	40%
Angiotensin Receptor Blocker (ARB)	60%
Diuretics	80%

Table 3: Left ventricular ejection fraction (LVEF), Natriuretic peptide (NP) levels, and Seattle Angina Questionnaire-7 (SAQ-7) scores before and after six months of ESCM supplementation.

		Average	Range	Difference	% Change
LVEF	**Pre**	42.5 ± 1.6	40-50	+8.6 ± 1.8*	20.3% ± 4.5
	Post	51.1 ± 1.6	49-55		
Natriuretic Peptides	**Pre**	1907.4 ± 78.6	1770-2001	-281.7 ± 83.5*	14.7% ± 3.3%
	Post	1625.7 ± 8.6	1542-1773		
SAQ-7	**Pre**	65.0 ± 2.1	62-68	+15.0 ± 3.8*	23.1% ± 6.3
	Post	80 ± 1.7	75-85		
	Post	28.8 ± 7.7	19-37		

*** p<0.001**

Discussion

The present study evaluated the effect of Stemregen Release, a proprietary blend of plant extracts known to promote ESCM, on patients with stable chronic congestive heart failure. The preliminary outcome demonstrated a significant improvement in cardiac function and a reduction in clinical heart failure symptoms, as indicated by improved ejection fraction and decreased biomarkers associated with myocardial stress. These findings suggest that daily administration of Stemregen Release over an extended period offers a beneficial effect on cardiac function and heart failure symptoms.

Previous studies utilizing stem cell injections for heart failure have shown variable outcomes, with modest improvements in myocardial function or no clinically significant benefit. Botleroo et al. [6] reviewed several trials employing different stem cell types such as bone marrow mononuclear cells (BMMCs) and mesenchymal stem cells (MSCs), noting that while many of these interventions were safe, the improvements in cardiac function were often limited and inconsistent.

For example, the Athena trials investigated the use of intramyocardial injections of adipose-derived stromal vascular fraction (SVF) cells in patients with ischemic heart failure and the results indicated a non-significant increase in maximum oxygen consumption during exercise treadmill testing in the treatment group [50]. In a controlled clinical trial, nine of 18 patients received intracoronary autologous bone marrow-derived mononuclear cells (BMMNC). After four years, the stem cell group exhibited slight improvement in ejection fraction (9.7%), along with reduced coronary plaque count, calcium scores, and plaques causing >50% stenosis [11]. In one prospective nonrandomized clinical trial with 24 patients with ischemic heart disease, intracoronary injection of BMSC led to a significant increase in ejection fraction (28.5%) and increase in infarct wall movement velocity, as well as reduction in infarct size [12].

Systemic intravenous injection of stem cells has demonstrated comparable outcomes. In patients with chronic stable heart failure,

intravenous administration of umbilical cord-derived MSCs (UC-MSCs) significantly improved left ventricular ejection fraction (LVEF; 7%), functional status, and quality of life [51]. Similarly, in nonischemic cardiomyopathy, intravenous administration of MSCs increased 6-minute walk distance and enhanced health and functional capacity [52]. These improvements in cardiac function are partially attributed to the anti-inflammatory effects of MSCs [53].

Granulocyte-colony stimulating factor (G-CSF), a cytokine known to mobilize stem cells, has been explored as a therapeutic agent in heart failure and ischemic heart disease. Despite the promising results in animal studies [23,25,28,29], the results in human trials have been mixed. Ripa and Kastrup [26] reported that G-CSF mobilization in acute myocardial infarction did not yield substantial improvements in myocardial recovery. Similarly, Hibbert et al. [36] in the CAPITAL STEM MI trial showed no conclusive benefit of G-CSF on myocardial function. Others have reported similar lack of significant benefits [54-57].

In contrast, Engelmann et al. [58] reported that G-CSF administration improved myocardial perfusion of the infarcted area (6.2%) and enhanced neovascularization. After a 9-month follow-up, G-CSF administration led to significant improvement in left ventricular ejection fraction (9%) in four patients with ischemic cardiomyopathy [59]. Follow-up after three months showed sustained improvement in left ventricular ejection fraction (LVEF; 5.4%) in the group receiving both G-CSF and MNC therapy at 3 months, which was maintained after 1 year. LVEF enhancement was associated with significant improvements in quality of life, exercise capacity, NYHA classification, and a reduction in N-terminal pro-brain natriuretic peptide levels [60]. Finally, after four G-CSF administrations, nine of twelve patients with ischemic heart disease showed significant improvements in LVEF (15%), six-minute walking distance (21%) and NYHA class, while none of the eight control patients exhibited changes in NYHA class over the same period [61].

Unfortunately, despite the promising results, multiple studies have linked G-CSF to notable risks that include increased alkaline phosphatase levels, myalgia and headaches, aortitis, interstitial pneumonitis, respiratory distress syndrome, thrombocytopenia, rare cases of spleen rupture and allergic reactions. In patients with coronary artery disease, G-CSF treatment has been associated with a heightened risk of restenosis and acute coronary syndromes due to its pro-inflammatory and pro-thrombotic effects [39,55,62].

Stemregen Release offers a safe, plant-based alternative for harnessing ESCM in heart failure treatment. The present exploratory study highlights the product's notable efficacy in improving myocardial function without the associated adverse effects. While some of the observed benefits are consistent with the effects of stem cell mobilization, no direct mechanistic conclusions can be drawn from this study. It is important to note that any reference to ESCM is based on previously reported effects of the product's ingredients and remains a hypothesis in the current context. Stemregen Release contains several plant extracts known to induce ESCM and increase circulating stem cell numbers. The mechanisms of action for some extracts have been partially elucidated. *Aphanizomenon flos-aquae* contains an L-selectin blocker, increasing circulating stem cells by 25% within one hour of consumption [41]. Panax notoginseng promotes ESCM by increasing serum Stem Cell Factor and reversing the SDF-1 gradient between bone marrow and blood [46]. The mechanism of action behind the mobilizing effects of *Aloe macroclada* and *Hippophae rhamnoides* remain unclear [42,43].

Stem cell mobilization induced by Stemregen Release may be an effective alternative for several reasons. Unlike G-CSF, which suppresses stromal cell-derived factor 1 (SDF-1) secretion, reducing stem cell homing to damaged myocardial tissue, Stemregen Release does not interfere with SDF-1 signaling, allowing for normal stem cell migration and retention [27]. Additionally, G-CSF causes a single sustained significant spike in circulating stem cells, whereas Stemregen Release triggers daily, transient smaller increases repeated over longer periods of time, providing sustained tissue repair [41]. Furthermore, G-CSF activates pro-inflammatory pathways in cardiac tissues, potentially limiting regenerative effects, while Stemregen Release includes anti-inflammatory plant extracts, fostering a more conducive environment for myocardial repair [63-66].

Overall, the findings of this exploratory study demonstrates that ESCM using Stemregen Release has the potential to enhance cardiac function in heart failure patients. ESCM is emerging as a promising, non-invasive therapeutic approach for heart failure and other degenerative diseases [47], particularly for those who are unresponsive to standard therapies or seeking adjunctive strategies, with a lower risk profile compared to conventional stem cell therapies. Further studies are warranted to fully characterize the therapeutic potential and broader applications of ESCM in other degenerative diseases, as well as animal studies to fully elucidate the mechanisms of action.

In summary, while this preliminary study demonstrates improvements in clinical parameters associated with heart failure, these findings remain exploratory. ESCM is the scientific rationale for choosing this intervention, but causality cannot be inferred from the present data.Larger, controlled studies incorporating mechanistic assessments are needed to determine the precise role of ESCM in these outcomes.

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