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Does Stem Cell Injection Improve Quality of Life in Patients with Cardiopathy Patients?

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A SELECTIVE EVIDENCE-BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Suwanee, Georgia

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ABSTRACT:

OBJECTIVE: The objective of this selective EBM review is to determine whether or not stem cell injections improve the quality of life in patients with cardiopathy.

STUDY DESIGN: Review of three randomized controlled trial (RCT) articles. All articles were published between 2012 – 2017 and were all printed in the English language.

DATA SOURCES: All three RCT articles were found through PubMed.

OUTCOMES MEASURED: One of the outcomes measured in each of the articles were improvement in quality of life in patients with cardiopathy. Among the three review articles, quality of life was measured using either the Kansas City Cardiomyopathy Questionnaire (KCCQ) and/or the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Questionnaires were given to patients at either three, six, and/or twelve months after stem cell or visually matched placebo injections. Higher scores for MLHFQ indicated a decrease in quality of life. Whereas, higher scores in the KCCQ indicated improvement in the quality of life.

RESULTS: All three studies used in this selective EBM review reported improvement in the quality of life at 3, 6, and/or 12-month assessment periods. Hare et al. study reported a p-value of 0.05 and 0.0167 versus baseline for the MLHFQ and KCCQ respectively. Similarly, the Hamshere et al. study also reported that a combination of G-CSF with IC BMC demonstrated an improvement the quality of life and reported a significant p-value of 0.005 at the one year assessment period. Improvement in quality of life was also reported in the Hare et al. study. A p-value of 0.009 was reported for autologous stem cell injections.

CONCLUSIONS: The three RCT used in this EBM review concluded that stem cell injections improved cardiac function resulting in the improvement of the quality of life in patients with cardiopathy.

KEY WORDS: cardiopathy, stem cell, stem cell injections, quality of life
INTRODUCTION

According to the CDC in 2015, cardiopathy is the leading cause of death in both genders and among most ethnicities in the United States.\textsuperscript{1,2} Cardiopathy is a broad term that is defined as any disease of the heart and includes but is not limited to heart failure, cardiomyopathies, arrhythmias or valvular diseases. Since cardiopathy encompasses a vast variety of heart diseases, this evidence-based medicine (EBM) review will focus on patients with heart failure.

Heart failure (HF) is a progressive condition where the heart is unable to pump enough blood to meet the body’s demand for oxygen.\textsuperscript{3} Heart failure can be either left-sided, right-sided or both. Some of the most common leading causes of heart failure are coronary artery disease (CAD), hypertension and myocardial infarction.\textsuperscript{3} It is known that after a myocardial infarction, cardiac cells die and the formation of scar tissue replaces the cardiac myocytes resulting in decrease heart function.\textsuperscript{4} In order to compensate for the decrease of function, the heart undergoes remodeling which leads to heart failure.\textsuperscript{4}

Approximately 5.7 million patients in the United States have heart failure and it has been projected that 8 million patients will be diagnosed with heart failure by 2030.\textsuperscript{5} According to the CDC in 2009, heart failure contributed to about one in nine deaths in the United States.\textsuperscript{6} The estimated annual cost of heart failure is $30.7 billion dollars and this total includes the cost of health services, medications, and missed days from work.\textsuperscript{6} The exact number of healthcare visits for heart failure annually is unknown as heart failure visits are accounted for in heart disease visits.\textsuperscript{7}

Stem cells are multipotent cells and can be isolated from many organs such as the umbilicus, bone marrow and pancreases.\textsuperscript{4} This EBM review will focus on the mesenchymal stem cells (MSC) originating from the umbilical cord and bone marrow as well as granulocyte
colony-stimulating factors (G-CSF). Under trauma or stressful events, stem cells enter the cell cycle and more cells are generated. Historically, it has been argued that unlike other organs, the heart does not self-renew after injuries because the heart lacked stem cells. However, with the discovery of stem cell niches in an adult heart, this theory was refuted. Even with the presence of stem cells, the heart fails to regenerate because the heart is composed of very little stem cells. MacLellan stated that the heart consists of very little stem cells because these immature stem cells lack the ability to fully contract. In order to properly pump blood throughout the body, the heart must be able to contract with maximum capability and therefore, is composed of very little immature stem cells. The limited amount of cardiac stem cells resulted in the proposal of stem cell injection in cardiopathy patients.

Stem cell injections are costly and the average cost of a single treatment for autologous stem cell is $7694.00 and $6038.00 for allogeneic cells. Current treatment of heart failure includes medications from classes of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers (BB), calcium channel blockers (CCB), diuretics and ionotropic agents such as digoxin, dobutamine, and dopamine. Other treatments include sodium restriction in the diet and daily physical activities. These current treatments are effective in supportive treatment and help decline the progression of heart failure. However, these treatment options do not improve cardiac function like stem cell injections. This systematic review will evaluate the improvement of the quality of life in patients with cardiopathy who received stem cell injections.

**OBJECTIVE**

The objective of this selective EBM review is to determine whether or not stem cell injections improved the quality of life in patients with cardiopathy.
METHODS

The criteria used for the selection of studies in this selective EBM centered on populations, interventions, comparisons, and outcomes. The population studied were patients older than eighteen years and diagnosed with heart failure (Table 1). The interventions were an injection of allogenic UC-MSC, allogenic and autologous bone marrow-derived stem cells, and granulocyte colony-stimulating factor (G-CSF) in the treatment groups. The controlled group received visually matched peripheral placebo injections. Comparison of improvement in the quality of life was made between patients that received stem cell or placebo injections. The outcomes were measured with either the Kansas City Cardiomyopathy (KCCQ) or Minnesota Living with Heart Failure Questionnaire (MLHFQ) at either three, six, or twelve months.

The research articles for this EBM review were selected based on similar inclusion criteria and the questionnaire used to measured improvement in the quality of life. All randomized controlled trial (RCT) articles were found through PubMed with a key word search consisting of “stem cells”, “heart failure”, “cardiopathy”, “quality of life”, “mesenchymal stroma cells” and “bone marrow stem cells”. All three RCT articles were published in peer-reviewed journals, after the year 2007, and in the English language. The summary of statistics used to report the data in all three RCTs were p-values and mean change from baseline.

Table 1 – Demographics and Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># pts</th>
<th>Age (yrs)</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>W/ D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barolucci, 2017 (1)</td>
<td>RTC</td>
<td>30</td>
<td>18-75</td>
<td>Chronic HFrEF w/ NYHA classification I to II and LVEF ≤ 40%</td>
<td>End-stage HFrEF, recurrent MI, uncontrolled V. tachycardia, malignant disease with life expectancy &lt; 1 yr, hematologic disease, recent cerebrovascular disease, serum creatinine</td>
<td>0</td>
<td>Intravenous infusion of allogenic UC-MSCs or placebo.</td>
</tr>
</tbody>
</table>
Casillas, Stem cell improve QOL in Cardiopathy, 4

<table>
<thead>
<tr>
<th>Study</th>
<th>RTC</th>
<th>Age</th>
<th>Diagnosis</th>
<th>HR Control</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hams here, 2015 (2)</td>
<td>RTC</td>
<td>60</td>
<td>54-57</td>
<td>Diagnosis of non-ischemic DMC w/no secondary cause, LVEF of 40%, symptoms classed as NYHA II or greater</td>
<td>Less than 18 years old.</td>
</tr>
<tr>
<td>Hare, 2012 (3)</td>
<td>RTC</td>
<td>31</td>
<td>21-90</td>
<td>Chronic ischemia, LV dysfunction secondary to MI, severe hypokinesis, 21 to 90 years old, LV ejection, EF less than 50%, eligibility for cardiac catheterization within 5 to 10 weeks</td>
<td>Noncardiac condition limiting life expectancy to &gt; 1 year, GFR &gt;50mL/min, serious radiographic contrast allergy, clinical requirement for coronary revascularization, life-threatening arrhythmia in absence of implanted defibrillator, malignancy within 5 years of screening</td>
</tr>
</tbody>
</table>

**OUTCOMES MEASURED**

The outcomes measured were based on a Patient-Oriented Evidence that Matters (POEM). This EBM review measured the outcome of improvement in quality of life in patients with cardiopathy that received stem cell injections. Among the three review articles, quality of life was measured using either the Kansas City Cardiomyopathy Questionnaire (KCCQ) and/or the Minnesota Living with Heart Failure Questionnaire (MLHFQ). The KCCQ is a twenty-three questionnaire where a higher score indicated improvement in the quality of life. The MLHFQ is a twenty-one questionnaire where a higher score indicated a decrease in quality of life. Questionnaires were given to patients at either three, six, and/or twelve months after stem cells or visually matched placebo injections.
RESULTS

Three RCT articles were compared and contrasted in this EBM review to determine if stem cell injections improve the quality of life in patients with cardiopathy diseases. Due to the lack of RCTs and research trials, this EBM does not differentiate between bone marrow, umbilical derived G-CSF stem cells. The focus of this EBM is about the improvement of quality in patients with cardiopathy diseases who received stem cell injections regardless of the origin of the stem cells. Improvement in quality of life was assessed using the MLHFQ and/or the KCCQ.

The MLHFQ is a 21-item self-administer questionnaire that evaluates the patient's improvement of quality of life by assessing the effects of heart failure on physical, socioeconomic and psychological aspects of life. Scores range from 0 to 105, where higher scores indicated a decrease in quality of life. The KCCQ is a 23-item self-administer questionnaire that measured the quality of life by focusing on areas such as physical limitation, symptoms, social limitation, symptom stability and self-efficacy. Higher scores on the KCCQ indicated an improvement in quality of life.

In the study performed by Bartolucci et al, 65 patients were assessed for eligibility and 30 were selected and randomized into two groups: treatment or placebo. Eligibility inclusion criteria consist of but are not limited to patients with heart failure with a reduced ejection fraction (HFrEF) of < 40% or a patient who meets the conditions of the New York Heart Association (NYHA) for classification I to III. Exclusion criteria consisted of patients with end-stage HFrEF or uncontrolled atrial fibrillation or ventricular tachycardia. A complete list of inclusion and exclusion criteria can be found in Table 1. Patients were randomly assigned via a computer-generated list to a treatment or a placebo group by a person unrelated to the study.
The control group in Bartolucci et al, received visually matched placebo injections while the treatment group received umbilical derived stem cell injections at 2mL/min via peripheral vein for 30 minutes on days 0, 15 and 90. Following completion of injections, all patients were assessed for quality of life at baseline, 3, 6 and 12 months with the MLHFQ and the KCCQ. Out of the 15 patients in the placebo group, one patient was excluded from the data due to cardiovascular complication resulting in death. Another patient died due to unrelated complications.

The MLHFQ reported that the placebo group showed no significant mean change from baseline or a statistically significant p-value in the placebo group during any assessment periods. The treatment group for MLHFQ reported a statistically significant p-value less than 0.05 at the 3 and 12 month assessment periods and a p-value less than 0.0167 in mean change from baseline at 6 months (Table 2). The placebo group in KCCQ stated a statistically significant p-value of < 0.05 at 3 and 6 months but not for 12 months in mean change from baseline. The treatment group in KCCQ reported a p-value <0.05 in mean change from baseline at 3 and 6 months and a statistically significant p-value <0.0167 at 12 months in mean change from baseline (Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>n</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLHFQ</td>
<td>Placebo</td>
<td>14</td>
<td>37.42±22.22</td>
<td>29.04±18.39</td>
<td>26.86±22.93</td>
<td>27.07±20.36</td>
</tr>
<tr>
<td></td>
<td>UC-MSC</td>
<td>14</td>
<td>53.21±30.25</td>
<td>30.50±23.76†</td>
<td>27.07±21.54*</td>
<td>31.21±26.66†</td>
</tr>
<tr>
<td>KCCQ</td>
<td>Placebo</td>
<td>14</td>
<td>69.92±21.24</td>
<td>78.08±15.94†</td>
<td>78.64±18.46†</td>
<td>75.46±22.43</td>
</tr>
<tr>
<td></td>
<td>UC-MSC</td>
<td>14</td>
<td>57.48±25.33</td>
<td>73.22±22.89†</td>
<td>74.99±20.70†</td>
<td>72.82±24.10*</td>
</tr>
</tbody>
</table>

MLHFQ indicates Minnesota Living with Heart Failure Questionnaire; KCCQ indicates Kansas City Cardiomyopathy Questionnaire; UC-MSC indicates umbilical cord – mesenchymal stromal cells; *P<0.0167 vs baseline; †P<0.05 vs baseline.

The data from both questionnaires reported statistically significant p-values of <0.05 or <0.0167 in treatment groups during all three assessment periods. Overall, the data reported from
both questionnaires strongly suggest that stem cell injections improve the quality of life in patients with cardiopathy when compared to the placebo group.

In the Hamshere et al. study, 258 patients were assessed; 198 were excluded and 60 patients were selected. Inclusion criteria for this study include but is not limited to left ventricular ejection fraction less than or equal to 45% and meets the NYHA classification II to IV. Exclusion criterion, less than 18 years old. Additional inclusion criteria can be found in Table 1. The 60 patients were randomized using a dedicated trial software system into four even groups of n = 15. The three treatment groups received either G-CSF, G-CSF and intracoronary (IC) serum, or G-CSF and IC bone marrow-derived cells (BMCs). The control group received visually matched placebo. The three treatment groups received five days of G-CSF injections and all groups were assessed at baseline, three months and 12 months. The data reported for the placebo and G-CSF treatment group decreased from n = 15 to n = 13 due to one patient withdrawal at the endpoint and another withdrawal at the 3-month assessment. The G-CSF & IC serum treatment group reported 2 patients died after the 3-month assessment. The G-CSF & IC BMC treatment group had one patient withdrawal and one patient declined the 1-year CT scan.

Significant p-values, listed in Table 3, were noted for the G-CSF group at both the 3- and 12-month assessment. No significant p-value were noted at either assessment point for the G-CSF & IC serum group. The lowest significant p-values calculated at both assessment points was for the G-CSF & IC BMC. The p-value for the 12-month assessment for the overall summary was 0.0053 and clinical summary noted a 0.0005 p value.

Table 3: Quality of life assessment of group p-values for KCCQ overall and clinical summary

<table>
<thead>
<tr>
<th>KCCQ Overall Summary</th>
<th>Placebo</th>
<th>G-CSF</th>
<th>G-CSF &amp; IC Serum</th>
<th>G-CSF &amp; IC BMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>53.39(-4.911-9.680)</td>
<td>50.80(37.48-64.12)</td>
<td>57.48(45.49-69.47)</td>
<td>42.29(29.20-55.78)</td>
</tr>
</tbody>
</table>
As expected, no improvement in quality of life was reported in the placebo groups. The data reported at both assessment periods for the G-CSF and G-CSF & IC BMC treatment groups suggest strong evidence that an improvement in quality of life was noted in these patients. Therefore, the usage of G-CSF in combination with IC BMC demonstrated improvement in quality of life in patients with cardiopathy when compared to all other treatment groups and the controlled group.14

In the Hare et al. study, 96 patients were assessed for eligibility and only 31 were selected.8 An inclusion criterion for selection consisted of but is not limited to left ventricular ejection fraction less than 50%. Exclusion criteria included malignancy within 5 years of screening or life-threatening arrhythmia. Additional inclusion and exclusion criteria can be found in Table 1. The eligible 31 patients were randomized into three groups of n = 10, 10 and 11. In this study, there is no control group and all three treatment groups received stem cell injections in three increasing dose of either 20 million, 100 million, or 200 million MSCs8. The three treatment groups were further randomized and subdivided into two groups of either n = 5 or 6 and were given autologous or allogeneic MSCs. Autologous stem cells were derived from the iliac crest four to six weeks prior to stem cell injections.8 All treatment groups were injected once with the specific dose level at ten different sites in the heart. The quality of life was
measured using the MLHFQ and was assessed at 6 and 12 months.\textsuperscript{8} Prior to the injection of 200 million autologous MSCs, one patient was excluded from the data due to a left ventricular thrombus resulting in $n = 5$ in all subdivided treatment groups.

The results for the three different doses of MSCs for allogenic MSCs were combined and insignificant $p$-values of 0.29 and 0.34 were noted for the 6 month and 12-month assessment periods respectively. Similarly, data from all groups that received autologous MSCs regardless of the dose level, reported statistically significant $p$-values of 0.005 at 6 months and a $p$-value of 0.009 as at the 12-month assessment period (Table 4).

Table 4: P-Value for MLHFQ for autologous vs. allogenic treatment groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous</td>
<td>43.6 (8.0)</td>
<td>$p$-value = 0.005</td>
<td>$p$-value = 0.009</td>
</tr>
<tr>
<td>Allogenic</td>
<td>38.9 (8.5)</td>
<td>$p$-value = 0.29</td>
<td>$p$-value = 0.34</td>
</tr>
</tbody>
</table>

95% CI; MLHFQ indicates Minnesota Living with Heart Failure Questionnaire.

Overall, the data consist of strong evidence that suggested stem cells, more specifically autologous than allogeneic stem cells, do improve cardiac function leading to an improvement in the quality of life in patients with cardiopathy.

**Safety, tolerability and adverse events**

All patients tolerated UC-MSCs injections well and no adverse events, injuries, or hypersensitivity reaction was reported in the Bartolucci et al. study. Similarly, no complications of G-CSF therapy injections were reported in the Hamshere et al. study. A total of 7 patients (15.6\%) did report long bone pain during therapy but this side effect was common and expected.\textsuperscript{14} As mentioned previously, two deaths were reported in the G-CSF and IC BMC group and both deaths were unrelated to the stem cell injections. Hare et al. study reported that in one patient, cell culture became contaminated where bone marrow aspiration of autologous MSC had to be repeated.\textsuperscript{8}
DISCUSSION

Depending on the severity, cardiopathy can severely influence a person’s quality of life by reducing a person’s ability to perform everyday activities. Current treatments only delay the progression of heart failure and temporarily improve a patient’s quality of life. Stem cells, on the other hand, have shown to improve cardiac function resulting in an improvement in the quality of life.

The objective of this EMB was to determine if stem cell injections, regardless of the origin of the stem cells, improve the quality of life in patients with cardiopathy. All three studies used in this selective EBM review reported improvement in cardiac function resulting in an increase in quality of life. Hare et al. study reported that the intervention of UC-MSC injections resulted in the improvement in left ventricular function resulting in an improvement in the quality of life in patients.\textsuperscript{8} Similarly, the Hamshere et al. study also reported that a combination of G-CSF with IC BMC demonstrated an improvement in cardiac function and symptoms resulting in an improvement in the quality of life.\textsuperscript{14} Improvement in quality of life with favorable improvement in functional capacity was also reported in Hare et al. study.\textsuperscript{8}

Limitations

Although stem cells were shown to be effective and safe in all three RCT articles, there are contraindications and limitations to stem cell injections. One limitation is that stem cells have not been FDA approved.\textsuperscript{15} A major concern for the FDA about allogeneic stem cells injections is incompatibility resulting in an autoimmune reaction that could lead to complications such as death.\textsuperscript{16} Other limitations included cost, tumor formation, administration site reactions and the ability of stem cells to travel via the bloodstream and multiply in an undesirable location.\textsuperscript{10,15}
The three RCT studies also had limitations within their own study. The sample size for all three trials were small which could have possibly favor improvement in quality of life and the inclusion criteria was extensive resulting in lack of similar patient population. The Bartolucci et al. study listed limitations such as software restraints, a response rate of 71% from the patients, and the large range of left ventricular volumes at baseline that could have favored the results of stem cell injections.12

**CONCLUSION**

Base on the results of the three RCT articles, stem cell injections has shown to improve the quality of life in patients with cardiopathy. The p-values reported were statistically significant indicating that the data reported did occur and is reliable. Although all three articles did not use the same type of stem cells, those used showed improvement in cardiac function which led to an improvement in the quality of life.

Even with statistically significant p-values, the usage of stem cell therapy is relatively new and additional research should be performed. The usage of similar stem cells in treatment groups should be unified to rule in the efficacy of one type of stem cell. Although stem cell injections were reported safe and well received in all three RCTs, the possibility of rejection and the adverse effect will always be present. If possible, future research can be performed on compatibility screening that limits rejection and immune response from the body. Overall, stem cell injection therapy sounds promising but before approval, many limitations will have to be resolved.
REFERENCES


