Is L-Carnitine Effective in Reducing Mortality After an Acute Myocardial Infarction?

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Is L-Carnitine effective in reducing mortality after an acute myocardial infarction?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirement For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not L-carnitine decreases mortality rates post MI.


DATA SOURCES: Three double blind, randomized controlled clinical trials comparing mortality rates in patients post MI who were treated with L-carnitine or a placebo. All articles were found using PubMed and EBSCO.

OUTCOMES MEASURED:
In the Singh et al. study the outcomes were total cardiac events that included death and nonfatal infarctions, cardiac enzymes activity, infarct size, and any complications that were measured by myocardial infarct size, cardiac enzyme levels of CK and CK-MB, radiology, and electrocardiographic. In the Colonna study, outcomes were: left ventricular dilation, end diastolic volume, systolic volume, incidence of death and heart failure at 6 months, and infarct size that were measured by an echocardiograph. In the Tarantini study, the outcomes measured were: combined occurrence of death and heart failure that were measured by deaths.

RESULTS: In the Singh et al. study the total cardiac events including nonfatal infarction and cardiac deaths were significantly fewer in the L-carnitine group compared to placebo in 28 days. In the Tarantini study, a reduction in mortality was seen in the L-carnitine arm of the study at 5 days. The Colonna study results shows L-Carnitine does not seem to be effective in reducing mortality in patients after AMI.

CONCLUSIONS: The results of these RCTs suggest that L-carnitine isn’t much more effective in reducing mortality rates after AMIs than the placebo. There was some evidence to suggest that L-carnitine may be effective in reducing mortality short-term after an AMI but not long term. The studies reviewed demonstrated statistically significant decreases in mortality only in the time frame directly following an AMI.

KEY WORDS: Myocardial infarction, L-Carnitine,
INTRODUCTION

Myocardial infarction (MI or heart attack) occurs when blood flow is blocked to an area of the heart muscle that causes ischemic damage or death to the myocardial cells. Myocardial infarctions are potentially fatal conditions that are among the leading causes of death in both men and women worldwide. Carnitine plays a critical role in energy production and is found in high concentrations in cardiac muscle\(^1\). This paper evaluates three randomized controlled trials (RCTs) comparing the efficacy of L-Carnitine in preventing mortality in patients post myocardial infarction.

This topic/question is relevant to patients, doctors, and physician assistant practice because it is common, costly and accounts for a significant amount of healthcare visits. Prevalence of myocardial infarctions increase with age. It is estimated that 60-65% of MIs occur in patients above 65 years old and 28-33% occur in patients above 75 years old. Eighty percent of all deaths related to myocardial infarctions occur in persons above 65 years of age\(^2\). Coronary heart diseases cost $108.9 billion each year in the US\(^3\). Coronary heart disease and myocardial infarctions account for a significant amount of healthcare visits: in 2010, AHA reports that 17.6 million people in the United States have coronary heart disease with 8.5 million having myocardial infarctions\(^4\).

Myocardial infarction is defined as a clinical (or pathologic) event caused by myocardial ischemia in which there is evidence of myocardial injury or necrosis. Detection of a rise and fall of cardiac biomarker values is a crucial criterion in the diagnosis of MIs. Additionally, at least one of the following criteria are also needed to verify the diagnosis: symptoms of ischemia, development of pathologic Q waves in the electrocardiography (ECG), new or presumed new significant ST segment-T wave changes or new left bundle branch block (LBBB), identification
of an intracoronary thrombus by angiography or autopsy, imaging evidence of new loss or viable myocardium or a new regional wall motion abnormality\(^4\).

The usual methods of treatments of myocardial infarction and coronary artery disease are: relief of ischemic pain and oxygen therapy, assessment of the hemodynamic state and correction of abnormalities, initiation of reperfusion therapy with primary PCI or fibrinolysis, antithrombotic therapy to prevent re-thrombosis or acute stent thrombosis, beta blocker therapy to prevent recurrent ischemia and arrhythmias, Coronary Artery Bypass Graft (CABG), and lifestyle modifications: diet, EtOH, smoking cessation, and weight loss\(^2\).

Carnitine is found in high concentrations in cardiac muscle and serves several important physiological functions in the heart\(^5\). This method of treatment is being proposed to determine if L-carnitine decreases infarct sizes because carnitine deficiency is more significant in the infarcted portion of the myocardium than in healthy myocardium. Studies have shown potentially beneficial effects with L-carnitine administration in improving clinical status and survival of patients post myocardial infarctions\(^4\).

OBJECTIVE

The objective of this selective EBM review is to determine whether or not L-carnitine decreases mortality rates post myocardial infarction.

METHODS

The RCTs analyzed patients who had an acute myocardial infarction within 8-10 hours of symptoms. The intervention studied in the RCTs was L-Carnitine. In the Singh et al. study, patients were given 1.98g/d of L-Carnitine\(^6\). In the Colonna et al. study, patients were given L-Carnitine 9g/d continuous IV for the first 5 days, then PO 2g TID for next 12 months\(^7\). In the Tarantini et al. study, patients were given L-carnitine 9g/d by continuous IV infusion for initial 5
days then 4g/d orally for next 6 months\(^8\). In all three RCTs, treatment groups received L-Carnitine compared to the experimental group who received a placebo at the same dosage schedules. The following are measured outcomes that were utilized: total cardiac events including death and nonfatal infarctions, cardiac enzymes activity, infarct size, and complications (heart failure, and left ventricular dilation).

Key words used in the searches were “L-Carnitine” and “Myocardial Infarction”. All articles were published in peer-reviewed journals in the English language. The articles were selected through PubMed and EBSCO; the selected articles were based on relevance to the clinical question and that the studies outcomes were patient oriented outcomes (POEMs). Inclusion criteria consisted of: patients who were judged to likely have an acute myocardial infarction with onset of symptoms in the preceding 12-24 hours. Patients had either persistent ST elevation of 0.2 mV or more in two or more contiguous precordial leads, elevated cardiac enzymes, and continuous typical chest pain for at least 30 minutes unrelieved by sublingual or IV nitrates. Exclusion criteria consisted of studies previous acute MI, valvular or congenital heart disease, cardiomyopathy, absence of sinus rhythm, LBBB, pregnant, severe comorbidities, greater than 80 years of age, and patients unwilling or unable to give consent. The summary of statistics reported or used were p values, RBI, ABI, and NNT.
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>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh (1996)</td>
<td>Randomized, double-blind, placebo controlled trial</td>
<td>101</td>
<td>Avg 40-50s y/o</td>
<td>Judge likely to have AMI with onset of sx in the preceding 24 hrs</td>
<td>Patients unable or unwilling to give consent, Admitted more than 24 hrs after onset of sx</td>
<td>0</td>
<td>oral L-Carnitine 1.98g/d</td>
</tr>
<tr>
<td>Colonna (2000)</td>
<td>Multicenter, randomized, double-blind trial</td>
<td>472</td>
<td>&lt; 80 y/o</td>
<td>Seen at an ICU within 24 h of having their first acute anterior MI</td>
<td>Previous acute MI, Valvular or congenital heart disease, Cardiomyopathy, Absence of sinus rhythm, Left bundle branch block, Pregnant, Concomitant conditions that could affect follow-up, and Participating in another clinical study</td>
<td></td>
<td>Carnitine 9g/d continuou s IV for the first 5 days, then PO 2g TID for next 12 months</td>
</tr>
<tr>
<td>Tarantini (2012)</td>
<td>Randomized, double-blind, placebo controlled trial</td>
<td>2,330</td>
<td>&lt; 80 y/o</td>
<td>Continuous typical CP for at least 30 min unrelieved by s.l. or IV nitrates, Onset of sx of AMI within 12 h before randomization, and Persistent ST elevation of 0.2 mV or more in two or more contiguous precordial leads</td>
<td>Age &gt;80 y/o, Valvular or congenital heart disease, HCM, Severe renal or hepatic disorder, comorbidity limiting the pt’s life expectancy, Alcoholism, Pregnancy or lactation, and Unwillingness to provide informed consent</td>
<td>1</td>
<td>L-carnitine 9g/d by continuou s IV infusion for initial 5 days then 4g/d orally for next 6 months</td>
</tr>
</tbody>
</table>
OUTCOMES MEASURED

Outcomes measured in the Singh et al. study were: total cardiac events including death and nonfatal infarctions, cardiac enzymes activity, infarct size, and complication were measured by myocardial infarct size, levels of CK and CK-MB, electrocardiographic, complications at 28 days follow up that included deaths, LV function, arrhythmia, nonfatal re-infarction, and total cardiac events. The Colonna et al. RCT study measured outcomes such as left ventricular dilation, end diastolic volume, systolic volume, incidence of death of heart failure at 6 months, infarct size, and residual stenosis that was measured by an Echocardiograph. The outcomes measured by Tarantini et al. RCT study outcomes were combined occurrence of death and heart failure that was measured by number of deaths at various times from randomization.

RESULTS

The three randomized-controlled trials compared the efficacy of L-Carnitine to placebo in preventing mortality in patients post myocardial infarction. In the study by Singh et al, total cardiac events, which were defined as cardiac deaths and nonfatal re-infarctions, were 15.6% in the L-carnitine group and 26.0% in the placebo group. There was no significant decrease in cardiac deaths with treatment with L-carnitine vs. placebo with $p>0.05$ and Confidence Limits (CL) (1.88, 0.22). There was a significant decrease in nonfatal re-infarctions with L-carnitine vs placebo with $p<0.05$, Confidence Limits (CL) (1.86, 0.17). There was also a significant decrease in total cardiac events with L-carnitine vs placebo with $p<0.05$ and Confidence Limits (CL) (1.62, 0.27). The treatment effects of L-carnitine on mortality post MI are listed in Table 2. The relative risk reduction (RRR) is -0.4% and the absolute risk reduction (ARR) is -10.4%. The numbers needed to treat (NNT) was -9. All data
were analyzed on the basis of intention to treat and the outcome analyses were incorporated for patients who were lost to follow up or died.

Table 2: Treatment effects of L-carnitine treatment post AMI on cardiac events

<table>
<thead>
<tr>
<th>CER</th>
<th>EER</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.26</td>
<td>0.156</td>
<td>-0.4</td>
<td>-0.104</td>
<td>-9</td>
</tr>
</tbody>
</table>

In the study by Taratini et al, at 6 months post MI the survival rate was not significantly increased for L-carnitine group vs placebo group as determined by p=0.48. But at day 5 post MI, the survival rate was significantly higher for the L-carnitine group vs placebo group with p=0.041. The cumulative mortality rate at various times are as follows: at 0-5 days the confidence interval (CI) was 0.37- 0.98 and p-value < 0.05; at 0-7 days the CI was 0.42- 1.05 and p-value > 0.05; at 0-15 days the CI was 0.54- 1.26 and p-value > 0.05; at 0-30 days the CI was 0.53- 1.16 and p-value > 0.05; at 0-60 days the CI was 0.56- 1.18 and p-value > 0.05; at 0-90 days the CI was 0.60- 1.22 and p-value > 0.05; and at 0-180 days the CI was 0.63- 1.24 and p-value > 0.05. The treatment effects of L-carnitine on mortality are listed in table 3. The relative risk reduction (RRR) is -0.12% and absolute risk reduction (ARR) is -1.3%. The number needed to treat (NNT) was -76. At 6 months, total of 142 patients out of 2,330 patients died. There were 67 patients that died the from the L-carnitine group which was a six-month mortality rate of 5.7% and the mortality rate of the placebo group was 6.5% at six-months that lead to a non-significant 12% reduction in mortality between L-carnitine and placebo (p=0.48). The significant decreases in mortality were in the earlier periods of the study. At the five-day end point, the mortality reduction was significant in the L-carnitine group of CI 0.37 and p-value=
0.041. One patient assigned to the placebo group was loss to follow up and therefore was excluded from all analyses and “worst-case” analysis was not done to those lost to follow up.

Table 3: Reduction in mortality after MI with treatment with L-carnitine

<table>
<thead>
<tr>
<th>CER</th>
<th>EER</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.105</td>
<td>0.09</td>
<td>-0.12</td>
<td>-0.013</td>
<td>-76</td>
<td>0.041</td>
</tr>
</tbody>
</table>

The study by Colonna et al, measures death rates between patients treated with L-carnitine vs. placebo during hospitalization and from discharge to 1 year follow up. During hospitalization 11 (4.7%) patients treated with L-carnitine died compared to 14 (5.9%) patients treated with the placebo. Between discharge and 1 year follow up, 10 (4.3%) patients treated with L-carnitine died compared to the placebo group where 13 (5.4%) patients died. The treatment effects of L-carnitine on mortality reduction are listed in Table 4. The relative risk reduction (RRR) is -0.2% and the absolute risk reduction (ARR) is -2.3%. The number needed to treat (NNT) was -43. None of the participants in the study needed to discontinue the treatment. “Worst-case” analysis was not done to those lost to follow up.

Table 4: Mortality reduction post MI with treatment with L-carnitine

<table>
<thead>
<tr>
<th>CER</th>
<th>EER</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.113</td>
<td>0.09</td>
<td>-0.2%</td>
<td>-0.023</td>
<td>-43</td>
</tr>
</tbody>
</table>

None of the participants were reported to have adverse events in the reviewed studies from treatment with L-carnitine.

DISCUSSION
This selective evidence based medicine review investigated three randomized controlled trials to determine whether or not L-carnitine decreases mortality rates post myocardial infarction. While the selected studies provided no definitive evidence that L-carnitine decreased long-term mortality rates post myocardial infarction but these studies did suggest that L-carnitine might be helpful with infarction size and early mortality rates.

In the Singh study et al, total cardiac mortality rates did not show a significant reduction in the L-carnitine group compared to the placebo group (p>0.05) but did show a significant reduction in cardiac events, which were defined as cardiac deaths and nonfatal re-infarctions. For nonfatal re-infarctions with L-carnitine vs. placebo, there was a statistically significant decrease (p<0.05). There was also a significant reduction in total cardiac events with L-carnitine treatment, (p<0.05). The relative risk reduction (RRR) was -0.4%, so there was a 0.4% decrease in adverse events with L-carnitine versus placebo. The absolute risk reduction (ARR) is -10.4%, so there was a 10.4% decrease in adverse events with L-carnitine versus nothing. These values are small and further demonstrate that L-carnitine is not much more effective than the placebo in reducing mortality after an AMI. The authors of the article stated that carnitine may inhibit free radical injury to the myocardium, so this can be protective for the myocardium and non-infarcted areas. The study also suggests that there was a significant reduction in cardiac enzymes like creatine kinase, creatine kinase-MB, and aspartate transaminase and a smaller increase in lactate dehydrogenase, indicating less cardiac necrosis in the L-carnitine group. Decreasing necrotic areas of myocardium is a major goal of treating AMI. Current methods (nitro, oxygen therapy, CABG, stent) of trying to restore oxygenated blood flow are currently the gold standard but more studies should be done to further evaluate the usefulness of L-carnitine. Limitations of the study
may have been the samples size, comorbidities of the patients, and time sensitive drug therapy after onset of MI could have impacted the outcome.

In the study by Colonna et al, there seems to be minimal benefit to using L-carnitine. The mortality rate during hospitalization was 4.7% when treated with L-carnitine compared to 5.9% when treated with the placebo. Also, the mortality rates after discharge to one year follow up period were 4.3% for L-carnitine group compared to the placebo group at 5.4%. The RRR and ARR were both small showing that L-carnitine is not much more effective than the placebo in reducing mortality post MI. The study suggests that long-term L-carnitine treatment limits left ventricular dilatation, which should help the patient to prevent future sequelae and even death from the AMI. Limitations to the study could have been different facilities MI protocols, patients’ comorbidities, and time sensitive drug therapy after onset of MI could have also impacted the outcomes.

The study by Taratini et al, showed the mortality rate at 6 months was 5.7% for the L-carnitine group and 6.5% for the placebo group. This was a non-significant, 12% reduction in long-term (baseline - 6 months) mortality (p=0.48) with L-carnitine vs. placebo. However, the short-term (day 5) post MI survival rate was significant increased for the group treated with L-carnitine group (p=0.041) as demonstrated by the cumulative mortality rate at 0-5 days. But as stated in results portion, the cumulative mortality rate at 0-7 days, 0-15 days, 0-30 days, 0-60 days, 0-90 days, and 0-180 days all showed p-value > 0.05 demonstrating a non-significant increase in those survival rates. RRR and ARR values were small and demonstrate that L-carnitine is not much more effective than the placebo in reducing mortality after an AMI. The NNT was 76 people to have a positive outcome. Limitations of the study could have been comorbidities, and time sensitive drug therapy after onset of MI could have impacted the
outcome. Another limitation is the study was conducted at different facilities that may have different MI protocols. The study was terminated early due to the lower than expected enrollment rate so the samples size could have been another limitation.

All three studies show some evidence of the usefulness of L-carnitine. It does not necessary decrease long-term mortality rates because some MIs may cause too much damage for the individual patient to recover from the event. Most medical professionals would agree decreasing infarcts sizes and cardiac enzymes, and preventing left ventricular dilatation will improve the chances of survival and quality of life for the patients post MI. It is common knowledge that “time is tissue” with cardiovascular events therefore, time to treatment and the size of the area of infarction may have a role in determining the treatment effects of L-carnitine.

CONCLUSION

There is some evidence to suggest that L-carnitine may be effective in reducing mortality short-term after an AMI but not long term. The studies reviewed demonstrated statistically significant decreases in mortality only in the time frame directly following an AMI. Because of these results, future studies on the effects of L-carnitine should be conducted focusing on its efficacy short term after an AMI. The flaws in the conducted studies may have been that they did not focus treatment on the short term, which is where L-carnitine appears to have the greatest treatment effect.
References


