Nutritional Treatments for Acute Myocardial Infarction

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Abstract
Acute myocardial infarction (MI) is one of the most frequent causes of death in the United States. The evaluation and treatment of acute MI in conventional medicine has focused primarily on anatomical and physiological factors that lead to impaired blood flow. Less attention has been paid to metabolic factors that may influence the vulnerability of the myocardium to ischemia and to various stressors. There is evidence that in some cases inefficient cellular metabolism, rather than the availability of oxygen and other blood-borne nutrients, is an important factor determining whether cardiac pathology will develop. Metabolic dysfunction could result from intracellular deficiencies of magnesium, coenzyme Q_{10}, carnitine, and certain B vitamins, nutrients which play a role in the synthesis of adenosine triphosphate (ATP; the body's main storage form of energy). In addition, increased oxidative stress may contribute to the pathogenesis of both MI-related myocardial damage and reperfusion injury. Consequently, administration of antioxidants might improve outcomes in patients with acute MI.

Numerous clinical trials have found parenteral administration of magnesium in the early stages of acute MI can substantially reduce the death rate. In addition, several trials have shown L-carnitine is beneficial in the treatment of acute MI. Other nutrients, such as vitamin C, vitamin E, and various B vitamins, may also be of value.
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Introduction

Acute myocardial infarction (MI; also called myocardial infarction or heart attack) is characterized by necrosis of a portion of the heart muscle. It is one of the most frequent causes of death in the United States and other developed countries. Coronary atherosclerosis is frequently an underlying factor in the pathogenesis of MI. The acute event is often triggered by rupture of an atherosclerotic plaque, leading to the formation of an occlusive thrombus and vasospasm, which interrupt the delivery of oxygen to the myocardial tissue supplied by that artery. Coronary artery spasm may also trigger an MI in patients who do not have atherosclerosis. Common causes of coronary vasospasm include variant angina (Prinzmetal's angina) and cocaine use.

Complications of MI include arrhythmias, heart failure, and cardiogenic shock, each of which can be fatal. Conventional treatment of acute MI includes restoration of blood flow as soon as possible with a fibrinolytic agent or surgery (angioplasty or coronary artery bypass grafting). Other treatments include morphine for pain relief, aspirin or other anti-platelet medication, beta blockers, and angiotensin-converting enzyme inhibitors. This article discusses the use of specific nutrients for the treatment of acute MI and its short-term complications. Secondary prevention of MI (i.e., interventions designed to prevent a second MI in individuals who have had a first MI) is beyond the scope of this article.

Myocardial Vulnerability: An Underappreciated Factor

The evaluation and treatment of acute MI in conventional medicine has focused primarily on anatomical and physiological factors that lead to impaired blood flow, while paying less attention to metabolic factors that may influence the vulnerability of the myocardium to ischemia and various stressors.[1] There is evidence, however, that MI and sudden coronary death are caused in part by factors other than ischemia.

One investigator took plastic casts of the coronary vasculature of patients who had died from acute MI or had died suddenly from presumed coronary causes. He found each coronary artery was connected to adjacent ones by

Key words: myocardial infarction, magnesium, MI, carnitine, L-carnitine, vitamin E, vitamin C, vitamin B6, pyridoxal 5'phosphate, P5P, I.V., intravenous, heart attack

numerous good-sized anastomoses (20-350 microns), many or most of which were too small to be visualized by coronary angiography. In 44 percent of cases in which an occlusion of one or more coronary arteries was observed, no downstream infarct occurred, suggesting collateral circulation was adequate to meet myocardial demand. In addition, in 53 percent of cases of acute infarct, no occlusive thrombus of the artery supplying the infarct was found.[2,3] Furthermore, there is evidence that some thrombi develop primarily after the onset of myocardial necrosis and are therefore not the cause of the infarction.[4] These findings suggest that many cases of MI and sudden coronary death develop independently of an acute occlusion.

Examination of myocardial tissue of men who died suddenly from presumed acute cardiac causes revealed an ongoing process of selective myocardial cell necrosis not localized to the distribution of any particular coronary artery. The patchy distribution and the morphological features of the necrosis, combined with the fact that the lesions occurred in some patients without significant epicardial coronary disease, suggest ischemia was not the cause of the lesions or of the sudden cardiac death.[5] In another study, histologic examination of myocardial tissue of men who died suddenly from acute MI revealed small foci of fibrosis in the uninfarcted myocardium indistinguishable from those in pigs, calves, and lambs with nutritional muscular dystrophy.[6]

These findings allow for the possibility that impaired or inefficient cellular metabolism, rather than the availability of oxygen and other blood-borne nutrients, is in some cases an important factor determining whether the myocardium will meet its energy demands and whether cardiac pathology will develop.[7] Metabolic dysfunction could result from intracellular deficiencies of nutrients such as magnesium, coenzyme Q_{10}, or carnitine, which play a role in the synthesis of adenosine triphosphate (ATP; the body's main storage form of energy).

Nutritional deficiencies, in addition to increasing myocardial vulnerability, might also lead to a cascade of events that can eventually result in an MI. For example, a deficiency of any nutrient that plays a role in ATP synthesis could lead to an accumulation of adenosine diphosphate (ADP) under conditions of increased energy demand, since the rate of conversion of ATP to ADP might exceed the rate of regeneration of ATP under those conditions. ADP triggers platelet aggregation, which can promote vasospasm, arterial inflammation, and thrombosis.

The importance of non-ischemic factors should therefore be kept in mind when considering a nutritional approach to treating acute MI.

Magnesium: A Cardioprotective Nutrient

Magnesium has a number of effects that would be expected to be useful in the treatment of acute MI. Magnesium inhibits platelet aggregation and platelet-dependent thrombosis,[8] promotes vasodilation and prevents vasospasm,[9] and has antiarrhythmic activity. In addition, as a cofactor in the synthesis of ATP, magnesium plays a major role in myocardial energy production.

Catecholamines, released in response to various types of stress, cause a loss of magnesium from the heart and increase urinary magnesium excretion. Magnesium deficiency, in turn, increases the amount of catecholamines released in response to stress and aggravates the cardiotoxic effects of epinephrine, thereby creating a vicious cycle of greater magnesium deficiency and an increasingly deleterious response to stress.[10,11] Ischemia also causes a loss of magnesium from myocardial tissue,[12] potentially increasing the vulnerability of the myocardium to the adverse effects of ischemia.

Animals fed a magnesium-deficient diet developed focal myocardial necroses that were scattered randomly throughout the myocardium. These pathological changes were aggravated by stress (exposure to cold temperatures), resembled the changes seen in men dying from cardiac causes, and were inhibited by magnesium supplementation.[13,14] Myocardial necroses induced in rats by restraint-stress were also reduced by intraperitoneal administration of potassium-magnesium aspartate.[15] In addition, cardiac necroses induced in rats by injection of epinephrine were exacerbated by magnesium deficiency and decreased by magnesium supplementation.[16]

In dogs, magnesium deficiency increased the size of myocardial infarcts induced by surgical occlusion

of the left anterior descending artery for one hour.[17] In pigs, MI was induced by arterial injury combined with mechanical occlusion of the left anterior descending artery, which stimulated thrombus formation. Intravenous administration of magnesium decreased infarct size by more than 50 percent and preserved ejection fraction.[18] In rats fed a standard diet and subjected to surgical occlusion of the left coronary artery, MI occurred in 100 percent of 16 animals. Oral administration of magnesium chloride for five days prior to surgical occlusion reduced the incidence of infarction to 29 percent.[19] Magnesium supplementation (as potassium-magnesium aspartate) also delayed the appearance of electrocardiographic ST-segment elevation in healthy volunteers during exposure to hypoxia. This protective effect was not associated with an increase in oxygen consumption, which suggests the benefit was due to improved myocardial metabolism.[20]

Magnesium deficiency (as demonstrated by an intravenous magnesium load test) was found to be common in patients with ischemic heart disease.[21] In addition, serum magnesium levels were significantly lower in patients hospitalized with an acute MI than in other hospitalized patients. The risk of developing cardiac arrhythmias during an acute MI was significantly greater in hypomagnesemic than in normomagnesemic patients.[22]

Magnesium: Positive Uncontrolled Trials

In two uncontrolled trials published in the 1950s, intramuscular administration of magnesium, beginning as soon as possible after the onset of symptoms, substantially decreased the death rate in patients suffering an acute MI.

More than 100 patients with coronary heart disease, of whom at least one-third had had an acute MI, received intramuscular injections of magnesium sulfate (0.5-1 g [2-4 mmol] every five days for a total of 12 injections). The death rate was less than one percent, compared with a death rate of 31 percent during the previous year in similar patients treated with anticoagulants but no magnesium.[23]

Sixty-four patients with acute MI or acute coronary insufficiency received intramuscular injections of magnesium sulfate. The initial dosage was 0.25-1 g (1-4 mmol) per day for an unspecified period of time, followed by unspecified lower doses. The mortality rate during the 4-6 weeks after the MI was 1.6 percent. In contrast, the mortality rate reported by other investigators for similar patients receiving conventional therapy was 19-50 percent.[24,25]

Magnesium: Positive Double-blind Trials

More recently, numerous double-blind trials have found intravenous administration of magnesium during the first 24-48 hours following acute MI significantly[26-30] or nonsignificantly[31,32] decreased mortality rate compared with placebo, with mortality reductions as high as 63-88 percent in some studies. The beneficial effect of magnesium appears to be due in part to decreased incidences of cardiac arrhythmias[33,34] and cardiogenic shock. Meta-analyses of randomized controlled trials found intravenous magnesium reduced the risk of death from acute MI by 39-69 percent.[35-37]

Patients (n=273) with suspected acute MI were randomly assigned to receive, in double-blind fashion, magnesium or placebo intravenously, immediately on admission to the hospital. The dose of magnesium was 50 mmol during the first 24 hours (30 mmol during the first six hours, 20 mmol during the next 18 hours) and 12 mmol during the second 24 hours. Among the 130 patients with a proven MI, the mortality rate during the first four weeks was 63.2-percent lower in the magnesium group than the placebo group (7% versus 19%; $p<0.05$). The incidence of arrhythmias requiring treatment was 55.3-percent lower in the magnesium group than the placebo group (21% versus 47%; $p=0.004$). Fewer patients in the magnesium group than in the placebo group died from cardiogenic shock (0 versus 7). In intent-to-treat analysis (including patients with and without a proven MI, and assuming all patients who did not have an MI survived at least four weeks), the mortality rate was 71-percent lower in the magnesium group than the placebo group (2.9% versus 10.2%). Among the 273 study participants, the proportion having a confirmed MI was 23.8-percent lower in the magnesium group than the placebo group (41.2% versus 54.1%),[26] a finding that suggests magnesium has a cardioprotective

effect in some patients with impending MI.

In a double-blind trial, 100 acute MI patients were randomly assigned to intravenous magnesium sulfate or placebo beginning within six hours of the onset of symptoms. The dose of magnesium was 50 mmol during the first 24 hours (30 mmol during the first six hours, 20 mmol during the next 18 hours) and 12 mmol during the second 24 hours. The mortality rate (4% versus 20%; 80% reduction; $p<0.05$) and the incidence of arrhythmias (8% versus 34%; 76% reduction; $p<0.01$) were significantly lower in the magnesium group than the placebo group.[27]

Patients (n=103) with acute MI were randomly assigned to receive, in double-blind fashion, intravenous magnesium sulfate or placebo for 48 hours. The dosage of magnesium was 25 mmol during the first three hours, 41.6 mmol during the next 21 hours (total, 66.6 mmol during the first 24 hours), and 25 mmol during the last 24 hours. In-hospital mortality was 88.2-percent lower in the magnesium group than in the placebo group (2% versus 17%; $p<0.01$). Of the original group of 115 patients admitted with a diagnosis of MI, 12 (10.4%) were subsequently found not to have had an infarction: 15.3 percent of those receiving magnesium and 5.4 percent of those receiving placebo. Based on that finding, the authors suggest magnesium therapy may have aborted an impending MI in some cases.[28]

In a double-blind trial, 194 patients with acute MI who were ineligible for thrombolytic therapy were randomly assigned to receive intravenous magnesium sulfate or placebo according to the protocol in the study described immediately above. In-hospital mortality was 74-percent lower in the magnesium group than the placebo group (4% versus 17%; $p<0.01$). The incidence of arrhythmias was also significantly lower in the magnesium group (27% versus 40%; $p=0.04$). Mean left ventricular ejection fraction at 72 hours (49% versus 43%; $p=0.01$) and at 1-2 months after hospitalization (52% versus 45%; $p=0.01$) was significantly higher in the magnesium group than the placebo group.[29] After a mean follow-up period of 4.8 years, all-cause mortality (18.8% versus 33.7%; 44% reduction; $p<0.01$) and cardiac mortality (12.5% versus 30.6%; 59% reduction; $p<0.001$) were significantly lower in the magnesium group than in the placebo group. Among patients still alive at follow-up, mean left ventricular ejection fraction was significantly higher (51% versus 44%; $p<0.05$) and the incidence of heart failure was significantly lower (3 versus 12 patients; $p=0.02$) in the magnesium group than the placebo group.[38]

In the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), 2,316 patients with suspected acute MI, with symptom onset in the preceding 24 hours, were randomly assigned to receive, in double-blind fashion, magnesium sulfate (8 mmol over five minutes, followed by 65 mmol over 24 hours) or placebo. One-third of the patients in each group received thrombolytic therapy and two-thirds received aspirin on admission. Myocardial infarction was confirmed in 65 percent of the patients in each group. In intent-to-treat analysis, 28-day all-cause mortality was 24-percent lower in the magnesium group than in the placebo group (7.8% versus 10.3%; $p=0.04$). The incidence of left ventricular failure was 25-percent lower in the magnesium group than the placebo group ($p<0.01$). The effect of magnesium on mortality was not modified by administration of thrombolytic agents or aspirin. Side effects of magnesium were transient flushing related to the rate of administration of the loading dose and an increased incidence of sinus bradycardia.[30]

In addition, intravenous magnesium therapy, as an adjunct to coronary angioplasty, improved left ventricular function and microvascular function in patients with acute MI. Japanese patients with a first acute MI (n=180) who had undergone successful coronary angioplasty were randomly assigned to receive intravenous magnesium sulfate or normal saline (control group). The dosage of magnesium was 8 mmol as a bolus prior to angioplasty, followed by 24 mmol over 24 hours. Mean pre-discharge left ventricular ejection fraction was significantly higher in the magnesium group than in the control group (63% versus 55%; $p<0.001$). Compared with controls, the magnesium group also showed significantly better regional wall motion, significantly smaller left ventricular end diastolic volume, and significantly higher coronary flow velocity reserve.[39]

Magnesium: Negative Studies

In contrast to these encouraging results, three studies found intravenous magnesium did not decrease mortality from acute MI.[40,41] One study (the Fourth International Study of Infarct Survival [ISIS-4]) was by far the largest of the magnesium trials.[42] In that study, 58,050 patients hospitalized up to 24 hours (median, 8 hours) after the onset of suspected acute MI participated in a randomized, 2 x 2 x 2 factorial study. The

treatment comparisons were oral captopril versus placebo, oral mononitrate versus placebo, and intravenous magnesium sulfate versus no magnesium sulfate (open control). The dosage of magnesium sulfate was 8 mmol as an initial bolus followed by 72 mmol over 24 hours. The five-week mortality rate was nonsignificantly higher by 5.5 percent in the magnesium group than in the control group (7.64% versus 7.24%). Magnesium treatment was associated with significant increases in the incidence of heart failure (12 more episodes per 1,000 patients) and cardiogenic shock occurring during or just after the infusion period (5 more per 1,000 patients). Magnesium treatment was also associated with a significant increase in the incidence of hypotension severe enough to require termination of treatment (11 more per 1,000 patients) and in the incidence of bradycardia (3 more per 1,000 patients).[42]

In the second negative study, 298 patients with suspected acute MI were randomly assigned to receive, in double-blind fashion, intravenous magnesium chloride (80 mmol over 24 hours; 40 mmol over the first 8 hours and 40 mmol over the next 16 hours) or placebo. Infusions were started immediately after admission to the coronary care unit. In-hospital mortality was nonsignificantly higher (by 19.8%) in the magnesium group than in the placebo group (12.1% versus 10.1%). Magnesium treatment resulted in a significant increase in the incidence of atrioventricular conduction disturbances.[40]

In the third negative study, 6,213 patients (median age, 70 years) with acute MI were randomly assigned to receive, in double-blind fashion, intravenous magnesium sulfate or placebo. The dosage of magnesium sulfate was 2 g over 15 minutes, followed by 17 g over 24 hours (total dose, 19 g; 76 mmol). After 30 days, the mortality rate did not differ between the magnesium and placebo groups (15.3% versus 15.2%).[41]

Because of the findings from the negative studies, intravenous magnesium did not ever gain a foothold in conventional medicine as a viable treatment option for acute MI.

Possible Explanation for the Conflicting Results

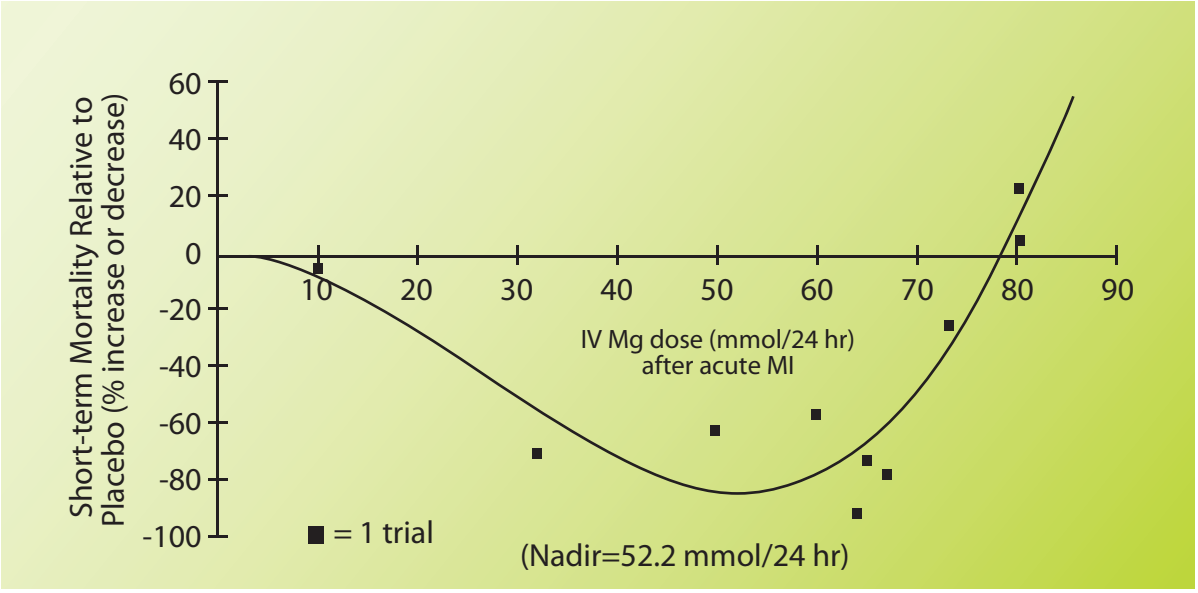
The most likely explanation for the discrepant results in the different magnesium trials is that the studies in which magnesium was not beneficial used excessive doses that were toxic to some individuals.[43,44] Administration of large intravenous doses of magnesium can cause hypotension, bradycardia, and conduction blocks, any of which could further compromise heart function and increase the risk of death in the setting of an acute MI. In most of the studies in which magnesium was beneficial, 50-66.6 mmol of magnesium was administered during the first 24 hours. An analysis of 10 clinical trials concluded that the optimum dosage for mortality reduction appeared to be 52 mmol per 24 hours (Figure 1).[45] In contrast, the amount of magnesium given during the first 24 hours was 80 mmol in two of the negative studies and 76 mmol in the third. Of note, in ISIS-4 magnesium therapy significantly increased the incidence of hypotension and bradycardia; and in one of the other negative studies[40] magnesium significantly increased the incidence of atrioventricular conduction disturbances. These findings support the idea that the dosage of magnesium was excessive. In ISIS-4, high-dose magnesium also increased the incidence of heart failure and cardiogenic shock, which could have resulted from increased myocardial necrosis secondary to hypotension

One positive trial (LIMIT-2)[30] used a relatively high dose of magnesium (73 mmol over 24 hours), which is not substantially lower than the 76 mmol given in one of the negative studies.[41] However, the patients in the negative trial were on average 8.6 years older than the patients in LIMIT-2, and they may have been less able to tolerate a large intravenous dose of magnesium. Moreover, the 24-percent mortality reduction in LIMIT-2 was considerably less than the mortality reduction in studies that used lower magnesium doses, which suggests 73 mmol over 24 hours was above the therapeutic window or was a toxic dose for a subset of the patients in LIMIT-2.

Using Magnesium in Clinical Practice

The bulk of the evidence indicates parenteral administration of appropriate doses of magnesium can markedly decrease mortality and improve other clinical outcomes in patients with acute MI. Magnesium appears to be beneficial when used as a primary therapy or as an adjunct to various conventional treatments. The optimal dosage of magnesium is not known, but it probably varies among different patients depending on such factors as lean body mass, age, renal function, and use of drugs that deplete (e.g., diuretics) or spare (e.g., angiotensin-converting enzyme inhibitors)[46] magnesium. The results of early uncontrolled trials

Figure 1. Intravenous Magnesium and Mortality after an Acute MI



In this analysis of 10 trials examining the effect of I.V. magnesium on short-term mortality after an acute MI, the optimum dose of magnesium was 52.2 mmol/24 hours.

Adapted from: Seeling MS, Elin RJ. Is there a place for magnesium in the treatment of acute myocardial infarction? *Am Heart J* 1996;132:471-477.

suggest that dosages well below those used in double-blind trials (such as 2-4 mmol per day for a few days) are effective. That possibility is supported by a double-blind trial in which a single intravenous dose of magnesium (9.6 mmol) reduced the incidence of potentially lethal arrhythmias by 58 percent in MI patients during the first 24 hours after admission.[33]

Magnesium should be considered for first-line treatment of acute MI patients who are not candidates for fibrinolytic therapy, such as those with uncontrolled hypertension, a recent stroke, or recent or current bleeding. In addition, further research should be conducted to determine whether magnesium is a viable alternative (as opposed to an adjunctive treatment) for patients who are candidates for fibrinolytic therapy. Although no head-to-head comparisons have been done, the reductions in mortality in the successful magnesium trials were at least as great as, and in some studies substantially greater than, the reductions in mortality in trials of fibrinolytic drugs. In addition, unlike fibrinolytic agents, magnesium does not cause cerebral hemorrhage or other types of bleeding. Furthermore, magnesium is far less expensive than fibrinolytic agents (less than $10 per dose, compared with more than $3,000 per dose for tissue plasminogen activator).

Potential adverse effects of intravenous magnesium include flushing, hypotension, and conduction blocks; these effects appear to be related to the dose and rate of administration. In patients who have intracellular potassium depletion, serum potassium levels may fall during intravenous magnesium administration, necessitating parenteral potassium treatment. It has been recommended that patients with significant sinoatrial or atrioventricular conduction disturbances or complete bundle branch block not receive parenteral magnesium. However, it is unclear whether that recommendation also applies to low-dose magnesium (such as 1 g per day of magnesium sulfate intramuscularly).

L-Carnitine

Carnitine plays a role in myocardial energy production by facilitating the transport of fatty acids into mitochondria. Myocardial carnitine depletion occurs during ischemia, and carnitine deficiency might exacerbate ischemia and contribute to the pathogenesis of MI. In rats, administration of carnitine protected against the

development of infarct-like myocardial necrosis induced by isoproterenol.[47] Low carnitine concentrations have been found in necrotic areas of myocardium of patients who had an acute MI, whereas carnitine levels were normal in surrounding healthy myocardial tissue. Carnitine concentrations were intermediate in the border zone between necrotic and healthy tissue, possibly indicating an area of reversible metabolic injury for which restoration of adequate carnitine levels might be beneficial.[48]

In clinical trials, treatment with L-carnitine significantly decreased the levels of creatine kinase-MB and troponin-I (markers of cardiac injury) and reduced the incidence of ventricular arrhythmias in patients with acute MI. In addition, administration of L-carnitine decreased the incidence of death and heart failure following acute MI and increased survival in patients suffering from cardiogenic shock, although most of the improvements were not statistically significant.

Patients (n=96) with non-ST elevation acute MI underwent percutaneous coronary intervention (PCI) and were randomly assigned to receive, in double-blind fashion, L-carnitine or placebo. The dosage of L-carnitine was 5 g given intravenously as a bolus 30 minutes before PCI, followed by 10 g per day intravenously for the next three days. Mean peak values for creatine kinase-MB at 12 and 24 hours after PCI were significantly lower in the L-carnitine group than in the placebo group ($p<0.01$). The mean peak value for troponin-I at eight hours was also significantly lower in the L-carnitine group than in the placebo group ($p<0.01$).[49]

In a double-blind trial, 56 patients with acute MI were randomly assigned to receive L-carnitine intravenously (100 mg per kg body weight every 12 hours for 36 hours, for a total of four doses) or placebo. On the second day of treatment, compared to placebo, L-carnitine reduced the number of episodes of ventricular tachycardia by 80 percent ($p<0.05$), the number of ventricular premature beats by 80 percent ($p<0.05$), and significantly reduced the amount of time with multiform or paired ventricular premature beats.[50]

In a double-blind trial, 2,330 patients with anterior acute MI were randomly assigned to receive placebo or L-carnitine within 12 hours of symptom onset. A dose of 9 g L-carnitine per day was given by continuous intravenous infusion for five days, then 4 g per day orally for six months. The mortality rate after five days was significantly lower by 39 percent in the L-carnitine group than in the placebo group (2.3% versus 3.8%; $p=0.04$). After six months, the composite endpoint of death and heart failure was nonsignificantly lower by 12 percent in the L-carnitine group than in the placebo group (9.2% versus 10.5%; $p=0.27$).[51]

Patients with a first acute MI (n=472) were randomly assigned to receive, in double-blind fashion, L-carnitine or placebo within 24 hours of the onset of chest pain. The dosage was 9 g per day intravenously for the first five days and 6 g per day orally for the next 12 months. The combined incidence of death and heart failure after discharge was nonsignificantly lower by 37.5 percent in the L-carnitine group than in the placebo group (6% versus 9.6%).[52]

Patients in cardiogenic shock after acute MI (n=27) received an intravenous bolus of 4 g L-carnitine followed by a continuous infusion of 6 g per day for the duration of the shock condition. The survival rate over a 10-day period was 77.8 percent, compared with an expected survival rate of 25-30 percent according to published data on similar patients.[53]

Based on the above findings, it would seem reasonable to administer L-carnitine to selected patients with acute MI.

Vitamin E and Vitamin C

Increased oxidative stress occurs during an acute MI and after reperfusion with a fibrinolytic agent. This increase in oxidative stress may contribute to the pathogenesis of both MI-related myocardial damage and reperfusion injury.[54-56] Because vitamins E and C have antioxidant activity they might minimize free radical-induced myocardial damage. Blood and leukocyte levels of vitamin C have been reported to fall significantly during the hours and first several days following an acute MI.[57,58]

In rabbits fed a standard diet, supplementation with vitamin E (50-200 IU per kg body weight per day) for 10 days prior to coronary artery ligation and reperfusion significantly decreased myocardial infarct size.[59,60] In dogs, daily supplementation with 500 IU vitamin E for two months reduced the mortality rate after coronary artery ligation and reperfusion.[61] In pigs subjected to coronary artery ligation and reperfusion, intravenous administration of 12,000 IU vitamin E three times during the week before ischemia and 4.4 g vitamin C intravenously before reperfusion significantly reduced the size of the infarct.[62]

In a randomized controlled trial, 61 patients with acute MI were assigned to receive conventional treatment alone (control group) or conventional treatment plus oral daily doses of 600 IU vitamin E and 600 mg vitamin C for 14 days. Vitamin supplementation prevented a deterioration of electrocardiographic findings, as measured by indices of the signal-averaged electrocardiogram. An abnormal signal-averaged electrocardiogram is associated with an increased risk of life-threatening arrhythmias and sudden cardiac death.[63]

In a larger double-blind trial, administration of vitamin E and C improved outcomes in patients with acute MI. In this trial, 800 patients (mean age, 62 years) were randomly assigned to receive vitamins E and C or placebo, beginning within 24 hours of the onset of symptoms and continuing for 30 days. Vitamin E was given at a dose of 600 IU per day orally and vitamin C was given at a dose of 1,000 mg intravenously over 12 hours, followed by 1,200 mg per day orally. All patients received conventional therapy. The primary endpoint was a composite of in-hospital cardiac mortality, nonfatal new myocardial infarction, life-threatening cardiac arrhythmia, shock, or pulmonary edema. The primary endpoint occurred 26-percent less frequently in the active-treatment group than in the placebo group (14% versus 19%; $p<0.05$). Thirty-day mortality was nonsignificantly lower by 22 percent in the active-treatment group than in the placebo group (4% versus 5.1%).[64]

A post-hoc analysis of this study revealed that the reduction in mortality was restricted to patients with diabetes. Among diabetics, 30-day mortality was 64-percent lower in the active-treatment group than the placebo group (8% versus 22%; $p<0.04$); among nondiabetics, treatment with vitamins E and C had no effect.[65] Inspection of the data from the original study revealed that active treatment decreased the incidence of the composite endpoint among nondiabetics, although it was unclear whether the reduction was statistically significant.

Although alpha-tocopherol was the form of vitamin E used in these clinical trials, it may be preferable to administer vitamin E in the form of mixed tocopherols. Vitamin E as it occurs naturally in food consists of four isomers: alpha-, beta-, gamma-, and delta-tocopherol. Human studies have shown supplementation with alpha-tocopherol can deplete gamma-tocopherol,[66] and there is evidence that gamma-tocopherol is as important as alpha-tocopherol for cardiovascular disease prevention. For example, gamma-tocopherol is more effective than alpha-tocopherol for scavenging peroxynitrite and other nitric oxide-derived oxidants,[67,68] which appear to be inflammatory mediators that promote the development of atherosclerosis. In addition, gamma-tocopherol may be a more potent anti-inflammatory agent than alpha-tocopherol since it inhibits cyclooxygenase-2 activity at a concentration at which alpha-tocopherol has no effect.[69] In rats, gamma-tocopherol was a stronger inhibitor of platelet aggregation than was alpha-tocopherol.[70] Furthermore, a metabolite of gamma-tocopherol functions as a natriuretic hormone[71] and, as such, may help prevent the development of heart failure.

B Vitamins

The mean plasma concentration of pyridoxal phosphate (the biologically active form of vitamin B_6) fell by 50 percent during the acute phase of an MI and returned to normal before discharge from the hospital.[72,73] In dogs, occlusion of the coronary artery reduced the concentration of flavin adenine dinucleotide (FAD; for which riboflavin is the cofactor) in the ischemic myocardium.[74] Several different B vitamins play a role in myocardial energy production and therefore might be useful in reducing myocardial vulnerability to ischemia. Clinical trials are warranted to determine whether administering B vitamins during the early stages of acute MI would improve outcomes.

Conclusion

The evidence reviewed in this article suggests that parenteral administration of magnesium in the setting of an acute MI could greatly decrease the death rate from this disease. Additional research should be conducted to determine whether magnesium is a useful adjunct or a viable alternative to fibrinolytic therapy. In addition, several studies have shown that L-carnitine, vitamin C, and vitamin E are beneficial in the treatment of acute MI. B vitamins might also be beneficial and warrant further research.

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