Creatine kinase and blood pressure: Clinical and therapeutic implications

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Chapter 7

Creatine and creatine analogues in hypertension and cardiovascular disease

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ABSTRACT

Background The creatine kinase system, the central regulatory system of cellular energy metabolism, provides ATP in situ at ATP-ases involved in ion transport and muscle contraction. Furthermore, the enzyme system provides relative protection from tissue ischaemia and acidosis. The system could therefore be a target for pharmacologic intervention.

Objectives To systematically evaluate evidence regarding the effectiveness of interventions directly targeting the creatine kinase system as compared to placebo control in adult patients with essential hypertension or cardiovascular disease.

Search methods Electronic databases searched: Medline (1950 – Feb 2011), Embase (up to Feb 2011), the Cochrane Controlled Trials Register (issue 3, Aug 2009), Latin-American/Caribbean databank Lilacs; references from textbooks and reviews; contact with experts and pharmaceutical companies; and searching the Internet. There was no language restriction.

Selection criteria Randomized controlled trials comparing creatine, creatine phosphate, or cyclocreatine (any route, dose or duration of treatment except for short-term use during cardiac surgery) with placebo; in adult patients with essential hypertension, heart failure, or myocardial infarction.

Data collection and analysis The outcomes assessed were death, total myocardial infarction (fatal or non-fatal), hospitalisation for congestive heart failure, change in ejection fraction, and changes in diastolic and systolic blood pressure in mm Hg or as percent change.

Results Full reports or abstracts from 1164 papers were reviewed, yielding 11 trials considering treatment with creatine or creatine analogues in 1474 patients with heart failure, ischemic heart disease or myocardial infarction. No trial in patients with hypertension was identified. Eleven trials (1474 patients, 35 years or older) comparing add-on therapy of the creatine-based drug on standard treatment to placebo control in patients with heart failure (6 trials in 1226/1474 patients), or acute myocardial infarction (4 trials in 220/1474 patients) or 1 in ischemic heart disease (28/1474 patients) were identified. The drugs used were either creatine, creatine phosphate (orally, intravenously, or intramuscular) or phosphocreatinine. In the trials considering heart failure all three different compounds were studied; creatine orally (Gordon 1995, Kuethe 2006), creatine phosphate via intravenous infusion (Ferraro 1996, Grazioli 1992), and phosphocreatinine orally (Carmenini 1994, Maggi 1990). In contrast, the
acute myocardial infarction trials studied intravenous creatine phosphate only. In the ischemic heart disease trial (Pedone 1984) creatine phosphate was given twice daily through an intramuscular injection to outpatients and through a intravenous infusion to inpatients. The duration of the study intervention was shorter for the acute patients, from a two hour intravenous infusion of creatine phosphate in acute myocardial infarction (Ruda 1988, Samarenko 1987), to six months in patients with heart failure on oral phosphocreatinine therapy (Carmenini 1994). In the acute patients the follow-up period varied from the acute treatment period (Ruda 1988) to 28 days after start of the symptoms (Samarenko 1987) or end of the hospitalization period (Zochowski 1994). In the other trials there was mostly no follow-up after discontinuation of treatment. Only three out of five trials in patients with acute myocardial infarction reported mortality outcomes, with no significant effect of creatine or creatine analogues (RR 0.94, CI: 0.46-1.93). In addition, there was no significance on the progression of myocardial infarction or improvement on ejection fraction, the main effect seems to be on improvement of dysrythmia.

**Conclusion** There is inconclusive evidence to decide on the use of creatine analogues in clinical practice. In particular, it is not clear whether there is an effect on mortality, progression of myocardial infarction and ejection fraction, while there is some evidence that dysrhythmia and dyspnoea might improve. However, it is not clear which analogue, dose, route of administration, and duration of therapy is most effective. Larger studies are needed to confirm the observations.
BACKGROUND

The creatine kinase system, the central regulatory system of cellular energy metabolism, is central to cardiovascular function. Creatine kinase regulates, buffers and transports, via creatine phosphate and creatine, ATP produced by glycolysis and oxidative phosphorylation, to sites of energy consumption such as myofibrils and membrane ion pumps. The enzyme substrate creatine is normally found in meat and fish, but it is also synthesized in the human body from dietary amino acids. Synthesis begins in the kidney with arginine and glycine forming guanidoacetic acid. This product is methylated in the liver, forming creatine (methylguanidine-acetic acid). Normal creatine plasma levels are 40-100 micromoles/liter (mcM/L); levels are about 25 mcM/L in vegetarians. The total adult body pool is approximately 120-140 grams. About 95% of body stores are found in muscle; creatine is also found in the liver, kidney, sperm, brain, eyes and the nervous system.

Myocytes use creatine (Cr) to make creatine phosphate (CrP) via creatine kinase. CrP is used to convert adenosine diphosphate (ADP) to adenosine triphosphate (ATP). By using hydrogen ions to make ATP, creatine kinase also buffers intracellular hydrogen ions associated with lactate production and muscle fatigue during muscle contraction. There is evidence that the creatine kinase system protects the cardiovascular system from ischaemia and increases contractility. Cardiovascular implications are that high blood pressure is proposed to occur earlier and to be more severe with greater activities of this enzyme system. On the other hand, low creatine kinase activities are associated with heart failure. The system could therefore be a target for pharmacologic intervention in cardiovascular disease.

Methods

Objectives

To systematically evaluate evidence regarding the effectiveness of interventions directly targeting the creatine kinase system as compared to placebo control in adult patients with essential hypertension or cardiovascular disease.

Criteria for considering studies for this review

Types of studies

Randomized controlled trials. There was no language restriction. Abstracts and reviews were excluded. Studies could have taken place in any care setting (in-patient, outpatient,
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day-care, or community). We did not include papers on the short-term use of creatine during cardiac surgery.

Types of participants
Adults (over 18 years of age) with cardiovascular disease (essential hypertension, heart failure or myocardial infarction) were considered.

Types of interventions
Studies examining agents directly interfering with the creatine kinase energy system, such as creatine, creatine phosphate or other creatine analogues versus placebo were considered. The intervention could be addressed by any route, in any dose and for any duration.

Types of outcome measures
The outcomes assessed were death, total myocardial infarction (fatal or non-fatal), hospitalisation for congestive heart failure, change in ejection fraction, and changes in diastolic and systolic blood pressure in mm Hg or as percent change.

Search methods for identification of studies
The Database of Abstracts of Reviews of Effectiveness (DARE) was searched for related reviews. The following electronic databases were searched for primary studies:

The Cochrane Central Register of Controlled Trials (CCTR) (2011, issue 1) Bibliographic databases, including MEDLINE (2005 – January 2011), EMBASE (2010 – January 2011), Latin American and Caribbean Health Sciences Literature (LILACS) (to August 2009), and the Cochrane Hypertension Group Specialised Register (all years). The Hypertension Group Specialised Register includes controlled trials from searches of AGRICOLA, Allied and Complementary Medicine (AMED), BIOSIS, CAB Abstracts, CINAHL, Cochrane Central Register of Controlled Trials, EMBASE, Food Science and Technology Abstracts (FSTA), Global Health, International Pharmaceutical Abstracts (IPA), LILACS, MEDLINE, ProQuest Dissertations & Thesis, PsycINFO, SCIRUS, and Web of Science. Other sources were handsearching of references from textbooks and reviews; reference lists of all papers and relevant reviews identified; contact with experts and pharmaceutical companies; and searching the Internet, in this order. No language restrictions were used.

Search strategy used for key databases, with results (February 2011):

Pubmed: [(creatine OR cyclocreatine OR phosphocreatin* OR guanidino OR Neoton)ti] AND (heart OR myocard* OR hypertensi* OR blood pressure OR cardiovascular); limit to "clinical trial" and "human"; 131 papers, 12 eligible trials; seven included in this review.
Embase: (creatine or cyclocreatine or phosphocreatin$ or guanidino or Neoton).m_titl. AND (heart or myocard$ or hypertensi$ or blood pressure or cardiovascular).mp. AND clinical trial; 104 papers, 10 new eligible trials not found in Pubmed systematic search; of which four are included in this review.

Lilacs: (creatine OR cyclocreatine OR phosphocreatin$ OR guanidino OR Neoton)ti AND (heart OR myocard$ OR hypertensi$ OR blood pressure OR cardiovascular); 13 papers, no eligible trial that was not already found in Pubmed or Embase.

Cochrane Library: [(creatine OR cyclocreatine OR phosphocreatine OR phospho/creatinine OR guanidino OR Neoton)ti] AND (heart OR myocard* OR hypertensi* OR blood pressure OR cardiovascular); 106 papers, no eligible trial that was not already found in Pubmed or Embase.

Handsearch: six new eligible trials, not found in any database with systematic searching. This was either because the clinical trial was absent from the database (EMBASE and Cochrane), or the “clinical trial” identifier was missing (MEDLINE). However, none of these papers fulfilled the inclusion criteria for this review.

Hence, in total, 11 trials were included, please see Figure 1.

Data collection and analysis
At least two reviewers independently assessed each eligible study unblinded. Risk of bias assessment was also performed independently by two reviewers. Disagreements were resolved through discussion. When there was no consensus between two reviewers, a third reviewer was asked for his or her opinion.

Judgement of validity
We included only randomized controlled trials.

Data collection
We developed a standard data abstract form for systematic collection of data on key trial characteristics, methodological quality, participants, comorbidity, intervention characteristics, drop outs, and outcomes. Two reviewers independently extracted data unblinded. Disagreements were resolved through discussion. We were unable to retrieve missing information.

Analysis
Statistical analysis was performed using Revman 5.1 software. Quantitative analysis of outcomes is based on intention to treat results (primary) and per protocol analysis (secondary). Our measure of effect for each study has been reported as relative risk for dichotomous data and weighted mean difference for continuous data.
Heterogeneity assessment
Chi square tests for heterogeneity were used to assess outcome data for computability with the assumption of a uniform risk ratio ($p > 0.05$). If statistical heterogeneity was found across studies, the sources of the heterogeneity were to be explored and decision was made if studies should be aggregated. If so, the random effect model would then be used.

Sensitivity analysis
If applicable, data was to be reanalyzed using both fixed and random effect models and using log odds ratio versus risk ratio.

Subgroup analysis
Separate analysis of results were planned for patients with hypertension, myocardial infarction, and heart failure, and for gender and ethnicity if data was available.

RESULTS

Trial retrieval
Full reports or abstracts from 1164 papers were reviewed, yielding 11 trials considering treatment with creatine or creatine analogues in 1474 patients with heart failure, ischemic heart disease or myocardial infarction. No trial in patients with hypertension was identified. Most trials were in English (n=6), Italian language (n=3), other trials were in Polish (n=1), or Russian (n=1). A flow chart for trial retrieval and selection is provided in Figure 1.

Description of included studies
All trials were randomized controlled trials of add-on therapy of the creatine-based drug to standard treatment, versus placebo. The methods, participants, interventions and outcomes of the included studies are listed in table ‘Characteristics of included studies’. Eleven trials (1474 patients, 35 years or older) comparing add-on therapy of the creatine-based drug on standard treatment to placebo control. Four trials (220/1474 patients) considered patients in the acute stage of myocardial infarction,8-11 six trials (1226/1474 patients) included patients with heart failure,12-17 and one (28/1474 patients) considered patients with ischemic heart disease.18 The drugs used were either creatine orally,14,16 creatine phosphate (CrP) (orally, intravenously, or intramuscular),8-11,13,15
or phosphocreatinine orally. In the heart failure trials all three different compounds were studied; creatine orally, creatine phosphate via intravenous infusion, and phosphocreatinine orally. The trials in patients with acute myocardial infarction only evaluated intravenous creatine phosphate. In the ischemic heart disease trial creatine phosphate was given twice daily through an intramuscular injection to outpatients and through an intravenous infusion to inpatients. The duration of the study intervention was the shortest for the acute myocardial infarction patients, ranging from a two hour to a 24hr intravenous infusion of phosphocreatine.

In contrast, intervention periods in the heart failure trials ranged between ten days and six months. In the acute myocardial infarction patients the follow-up period varied from the acute treatment period to 28 days after start of the symptoms, between 24-30 days after start of the symptoms, or end of the hospitalization period. In the heart failure trials there was mostly no follow-up after discontinuation of treatment. Data in square brackets are standard deviations, unless otherwise specified.

**Description of excluded studies**

Sixteen studies were excluded because they were not randomised controlled trials. A table with characteristics of excluded studies is provided online.

**Risk of bias in included studies**

The results of the Risk of Bias assessment for each trial are outlined under Characteristics of the included studies, provided online. Figure 2 shows an overview of all trials. All trials were randomized controlled trials of add-on therapy of the creatine-based drug to standard treatment, versus placebo. Ten studies had a parallel design and two studies were crossover studies. Three trials mentioned method of randomization. Allocation concealment was adequate in two trials and was unclear in ten trials. Blinding was adequate in six trials and was unclear in two trials. In the remaining four studies blinding was not adequate. Incomplete outcome data were addressed in six trials. Ten trials were free of selective reporting, in two trials this was not clear. None of the 11 trials were free of “other bias”. Please see the Risk of bias in included studies table online for further details.
Figure 1. Flow chart.

Reports retrieved in databases N=1444

Duplicate reports N=280

Abstracts evaluated N=1164

Excluded trials N=810
No trials of guanidino compounds in cardiovascular disease

Full reports evaluated N=354

Excluded reports N=333
No randomized controlled trials of guanidino compounds in cardiovascular disease

Eligible trials N=21

Excluded trials N=810
No trials of guanidino compounds in cardiovascular disease

Total eligible trials N=26

Nonelectronic search N=5*

Handsearching, contact with authors

Total included trials N=11
Acute myocardial infarction (N=4), heart failure (N=6), ischemic heart disease (N=1)

Effects of interventions

Trials in patients with hypertension

No randomized clinical trials were identified in patients with hypertension.

Trials in patients with acute myocardial infarction

1. Mortality. Only two out of four trials in patients (n=134) with acute myocardial infarction reported mortality outcomes during hospitalisation, with no significant difference between creatine analogues and placebo.\textsuperscript{10,11} Samarenko 1987 reported a mortality rate of 10% of the patients in the CrP group (n=30) with 17% in the control group (n=30), that did not reach statistical significance with this small sample size ($p>0.05$).\textsuperscript{10} Zochowski 1994 reported a 2.1% mortality rate in the intervention group (n=47), according to the authors, this was due to thrombolytic treatment complications; and no deaths in the control group (n=27).\textsuperscript{11} Pooling this data yielded a point estimate for the relative risk of 0.94 (CI: 95% 0.42-2.09), with this small samples size (Figure 3).

2. Hospitalisation for congestive heart failure. None of the acute myocardial infarction trials reported hospitalisation for congestive heart failure.

3. Total myocardial infarction (fatal or non-fatal). Data were inconclusive, in that Pedone 1984-2 measured the progression of myocardial infarction scintigraphically in the intervention vs the placebo group between day 2-6 vs day 24-30 after the onset of symptoms.\textsuperscript{8} They found that the number of segments that were partially or totally revascualized between day 24-30, were 15/40 (38%) with creatine
phosphate (n=13) vs 5/46 (11%) with placebo (n=13). In addition they reported new abnormalities in 2/40 (5%) in the intervention vs 7/46 (15%) in the placebo group.\textsuperscript{8} However, Samarenko 1987 reported no significant differences in perfusion at day 27 or 28: the final size of the region of the myocardial perfusion defect was 20(2)% of the myocardium in the intervention group (n=30) vs 23(2)% in the control group (n=30) (p>0.10).\textsuperscript{10}

4. **Changes in diastolic and systolic blood pressure.** None of the acute myocardial infarction trials reported changes in blood pressure.

5. **Changes in ejection fraction.** None of the acute myocardial infarction trials reported changes in ejection fraction.

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**Figure 3. Phosphocreatine versus placebo. Outcome: mortality.**

**Trials in patients with heart failure**

1. **Mortality.** None of the heart failure trials reported mortality outcomes.

2. **Hospitalisation for congestive heart failure.** None of the heart failure trials reported hospitalisation for congestive heart failure.

3. **Total myocardial infarction (fatal or non-fatal).** None of the heart failure trials reported total myocardial infarction.

4. **Changes in diastolic and systolic blood pressure.** None of the heart failure trials reported changes in blood pressure.

5. **Changes in ejection fraction.** Five trials reported ejection fraction as an outcome. Two out of five reported a significant effect of intervention.\textsuperscript{12,13} Carmenini 1994 reported a significant improvement from 35.9% ejection fraction at baseline to 40.5% after six months in the intervention group (n=39) that were reported to be significantly different (p<0.001) from the placebo group (n=40), although the
data of the placebo group were not shown. Ferraro 1996 reported a significant improvement with creatine phosphate (n=13) vs placebo after acute and short term treatment baseline: CrP 48(SD12)% vs placebo 50(12)%; acute: 53(12) vs 48(10)%; short term: 52(11) vs 48(12)%. However, we could not reproduce the authors' significant results. Out of the three remaining papers, two reported no significant effect of the intervention. Gordon 1995 after 10 days of treatment (no outcome data specified) and Kuethe 2006 after six weeks of treatment (Creatine 30(9)% vs placebo 29(8)%, n=13 in each group). Finally, Maggi 1990 did not report the difference between phosphocreatinine vs placebo. In conclusion, no study showed clear effect on ejection fraction.

Other outcomes as reported in publication of the included trials
The following outcomes were not prespecified in the review protocol, but were reported by authors.

Electrocardiographic findings
Reduction in dysrhythmia was found in the following trials. Three out of the four acute myocardial infarction (AMI) trials reported dysrhythmia as an outcome, with all three reporting a significant reduction in favour of the active intervention. Ruda 1988 reported a reduction in the total number of ventricular premature beats (VPBs) in the creatine phosphate group (n=30) vs placebo (n=30) with Holter monitoring (24hr ECG) during the 2hr treatment (CrP 690 (179) vs placebo 2468 (737), p<0.02). Samarenko 1987 showed a decreased frequency of ventricular extrasystoles in the intervention group (n=30) vs the control group (n=30) during Holter monitoring simultaneously with treatment on the first day (CrP 690 (179) vs placebo 2468 (737), p<0.02), without a significant decrease in supraventricular extrasystoles. Zochowski 1994 showed a significant difference in percentage reduction of dysrhythmia (not further specified) in CrP treated patients (n=47) vs controls (n=27) during Holter monitoring of the first 24hrs after the AMI (CrP -96.3% vs placebo -29.7%), but did not mention a P-value. Furthermore, a reduction in dysrhythmias was found in the single trial including patients with ischaemic heart disease and in two of the six heart failure trials. Pedone 1984 reported a significant reduction in the number of VPBs in the CrP intramuscular group (n=10) and the CrP intravenously group (n=18) compared to placebo (resp. n=10 and n=18) with Holter monitoring on the 10th day (CrP im -31.4% p<0.05, CrP iv -33.4% p<0.001). Grazioni 1992 showed a significant difference in percentage reduction of
VPBs in the CrP group (n=167) compared to placebo (n=150) after 15 days of treatment (CrP 68%, placebo 57%, \( p<0.05 \)). Maggi 1990 reported a reduction in the number dysrythmias and atrioventricular blocks in the patients receiving creatine phosphate (n=30) compared to placebo (n=30) (CrP 50%, placebo 30%), but data on the exact time of measurement during the intervention period was not given.

**Dyspnoea and orthopnoea**

Four of the heart failure trials reported improvement in dyspnoea and orthopnoea. Carmenini 1994 reported a reduction in dyspnoea (38.3%), orthopnoea (37.8%) and cough (32.8%) after six months in favour of the phosphocreatinine treatment (n=39), which all significantly differed from placebo (n=40) \( (p<0.001) \). In addition, Ferraro 1996 reported a significant improvement of symptoms in the creatine phosphate group (n=13) compared to the controls (n=13) \( (p<0.01) \), but did not further detail this data. Furthermore, Grazioli 1992 reported significant differences in dyspnoea after the 45 day treatment with creatine phosphate measured with a self-monitoring four point scale: in the intervention group (n=508) 7% reported moderate to severe dyspnoea vs 23% in the control group (n=499) on the 45 day \( (p<0.001) \). Finally, Maggi 1990 reported improvement on dyspnoea in favour of creatine phosphate (n=30) compared to controls (n=30), but not further detailed the data or mentioned the statistical significance. In contrast, Kuethe 2006 reported no significant differences on the Borg Scale of dyspnoea (measuring exhaustion on exercise) between creatine (n=13) and placebo (n=13), but did not provide further details.

**DISCUSSION**

High activity of the creatine kinase energy system has been associated with a greater risk to develop high blood pressure. On the other hand, too low activity might lead to heart failure and myocardial infarction. Although there is evidence that the creatine kinase system has a crucial role in the energy homeostasis, cardiovascular contractility, and ischaemic resistance, to our knowledge, the existing evidence on drugs directly targeting this system in humans has not been systematically reviewed previously. In this review, we found no trials of drugs targeting the CK system in patients with hypertension. The existing trials considered myocardial infarction and heart failure mainly. We found little evidence of a beneficial effect of creatine and creatine analogues in the prespecified outcomes, including ejection fraction and mortality. Pooling of the data resulted in a
point estimate of 0.94 for mortality without evidence of heterogeneity, but this outcome did not reach statistical significance. With no significance on the progression of myocardial infarction or improvement on ejection fraction, the main effect seems to be on improvement of dysrhythmia. Ventricular premature beats, ventricular extrasystoles and atrioventricular blocks were reported to be significantly reduced with the use of creatine phosphate or phosphocreatinine. Limitations of this review are that given the small sample size of the discussed trials and the clinical heterogeneity in patients, duration, mode of treatment (oral, intramuscular, or intravenous), and the drugs used (creatine, creatine phosphate, and phosphocreatinine), larger clinical studies are needed to confirm these observations. In particular, the potential effect on mortality needs further study with a larger sample size. The importance of the creatine kinase system for cardiovascular functions renders the system an interesting therapeutic target for drug intervention in cardiovascular disease.

CONCLUSIONS

Implications for practice
In our opinion, there is inconclusive evidence to decide on the use of creatine analogues in clinical practice. In particular, it is not clear whether there is an effect on mortality, progression of myocardial infarction and ejection fraction. While there is some evidence that dysrhythmia and dysnoea might improve. However, it is not clear which analogue, dose, route of administration, and duration of therapy is most effective.

Implications for research
Larger clinical studies are needed to confirm the observations of beneficial effects of supporting the creatine kinase system with creatine analogues in heart disease.

The importance of the creatine kinase system for cardiovascular performance under high energetic demands, renders the system an interesting target for therapeutic interventions in cardiovascular disease.
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