Effect of oral L-arginine supplementation on blood pressure: a meta-analysis of randomized, double-blind, placebo-controlled trials


CRD summary
The review concluded that oral L-arginine supplementation significantly lowered both systolic and diastolic blood pressure. The review was generally well conducted, but limitations in the evidence base and lack of precision suggest the authors’ conclusions should be considered tentative.

Authors’ objectives
To assess the effect of oral L-arginine supplementation on blood pressure.

Searching
PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and the ClinicalTrials.gov databases were searched up to June 2011 for relevant studies; search terms were reported. The reference lists of retrieved studies were also searched.

Study selection
Randomised placebo-controlled trials (RCTs) of double blind design that used oral L-arginine supplementation as intervention and reported the net changes of blood pressure were eligible for the review. Studies were excluded if they had a duration of intervention less than 1 week, had L-arginine administered by infusion or used L-arginine as part of the intervention.

In the included studies, the mean age of participants ranged from 21 to 66 years and approximately two thirds of participants were female. A few participants were considered healthy; the remainder had either hypercholesterolaemia, type 2 diabetes mellitus, peripheral arterial occlusive disease, gestational hypertension, coronary artery disease or polycystic ovarian syndrome. Most participants were considered normotensive; in one trial, results were presented separately for normotensive and hypertensive participants. In two trials, some participants were receiving concurrent hypertensive drugs, with a greater proportion in the control arms. Dose of L-arginine ranged from 4 to 24g/day, with a median of 9g/day. The duration of the intervention ranged from two to 24 weeks, with a median of four weeks. Five studies had blood pressure as the primary outcome. Adverse events were reported in some of the trials.

Two reviewers independently selected studies for the review, with disagreements resolved by discussion.

Assessment of study quality
Studies were assessed for quality using the 5 point Jadad scale; criteria included randomisation, blinding and withdrawals.

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Data extraction
Data were extracted on net change in blood pressure (systolic and diastolic) and, where necessary, standard deviations were estimated from standard errors, confidence intervals (CIs) and p values or computed using the Follmann method. For parallel trials, the net changes were calculated by the difference (intervention minus control) of the changes (final values minus baseline values) of the mean values. For crossover trials, the net changes were calculated as the difference of mean values at the end of the intervention and control periods. Mean differences, with 95% confidence intervals were also calculated.

Two reviewers independently extracted data for the review, with disagreements resolved by discussion.

Methods of synthesis
Studies were pooled in meta-analyses and summary weighted mean differences (WMDs), with 95% confidence
intervals, were estimated. Heterogeneity was assessed using the $\chi^2$ test (with $P<0.1$ as the significance level) and quantified using the $I^2$ value (with $I^2>50\%$ indicating substantial heterogeneity). A random-effects model was used where heterogeneity was identified; otherwise, a fixed-effect model was used. Sensitivity analyses were undertaken to explore potential sources of heterogeneity and test the robustness of the results, according to magnitude of blood pressure reduction, duration of intervention and use of antihypertensive medication. The influence of individual studies on the overall results was assessed by omitting each study in turn. Meta-regression analyses were undertaken to assess whether blood pressure reductions were related to trial characteristics, including L-arginine dose, intervention duration and baseline blood pressure levels. Publication bias was assessed by Begg’s test and Egger's test at the $P<0.01$ level of significance.

**Results of the review**

Eleven RCTs (387 participants, ranging from 12 to 79) were included in the review. Nine studies had a parallel group design and two studies had a crossover design. Jadad scores ranged from 3 to 5.

Compared to placebo, oral L-arginine was associated with a significant reduction in systolic blood pressure (WMD -5.39 mmHg, 95% CI -8.54 to -2.25; significant heterogeneity: $I^2=73.3\%$; 11 studies) and a significant reduction in diastolic blood pressure (WMD -2.66 mmHg, 95% CI -3.77 to -1.54; no significant heterogeneity; $I^2=34.4\%$; 11 studies).

Adverse events (measured in six trials) were not observed in four trials; in the other two, some participants experienced diarrhoea.

There was no evidence of publication bias by Begg's or Egger's tests.

Sensitivity analysis, with the exclusion of two trials which showed large systolic blood pressure reductions with L-arginine intervention, eliminated the heterogeneity but did not markedly change the overall result. Other sensitivity analyses also did not markedly change the overall blood pressure estimates. The results of metaregression suggested that blood pressure reductions were not related to L-arginine dose, intervention duration or baseline blood pressure levels. However, for participants with higher systolic blood pressure at baseline, there was a trend towards greater reduction in systolic blood pressure ($p=0.13$).

**Authors' conclusions**

Oral L-arginine supplementation significantly lowers both systolic and diastolic blood pressure.

**CRD commentary**

The review addressed a clear research question, supported by appropriate inclusion criteria. A range of relevant sources were searched to identify studies, but the authors stated that no specific attempts were made to find unpublished studies, so it was possible some studies may have been missed. Publication bias was assessed using formal tests and no evidence was found but there were too few studies for this method to reach robust conclusions. Appropriate methods were used throughout the review, which minimised the chance of reviewer error or bias.

A valid tool was used for quality assessment and overall scores suggested the studies were of reasonable quality, but some individual quality items were not always reported. The included studies generally had small sample sizes, so the potential for confounding factors influencing the results could not be excluded. Participants generally had a range of health conditions which limited generalisation of the findings. The included studies had a short duration of treatment, so long-term effects and safety of the intervention was not clear. Synthesis of the studies and assessment and investigation of heterogeneity were appropriate. The review was generally well conducted, but limitations in the evidence base and lack of precision suggest the authors' conclusions should be considered tentative.

**Implications of the review for practice and research**

**Practice:** The authors stated that the adoption by hypertensive individuals of a healthy diet that contains L-arginine rich foods may contribute to hypertension prevention.

**Research:** The authors stated that further large scale long term RCTs were required to confirm the blood pressure-lowering effect of L-arginine supplementation, particularly in hypertensive populations.
Funding
Nestec Ltd, Vevey, Switzerland.

Bibliographic details

PubMedID
22137067

DOI
10.1016/j.ahj.2011.09.012

Original Paper URL
http://www.ahjonline.com/article/S0002-8703(11)00697-1/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Oral; Adult; Aged; Antihypertensive Agents /administration & dosage; Arginine /administration & dosage; Blood Pressure /drug effects; Dietary Supplements; Double-Blind Method; Female; Humans; Hypertension /drug therapy; Male; Middle Aged; Randomized Controlled Trials as Topic; Young Adult

AccessionNumber
12012000051

Date bibliographic record published
28/03/2012

Date abstract record published
27/07/2012

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.