Therapeutic Benefits of L-Arginine: An Umbrella Review of Meta-analyses

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ABSTRACT

Objective: L-Arginine is a semi-essential amino acid that is the substrate for nitric oxide production by vascular endothelial and immune cells. Nitric oxide production by these cells is essential for both blood pressure regulation and immune regulation. However, there is much discrepancy in the literature when it comes to randomized controlled studies, and so this umbrella review of published meta-analyses was performed to examine the efficacy of L-arginine's role as a therapeutic agent.

Methods: There was an overall search of the literature from January 1, 1980 through December 31, 2015 of three separate databases—PubMed, Cochrane Library, and Cumulative Index to Nursing and Allied Health Literature—using the following search strategy: (arginine) AND (meta-analysis OR systematic review). Only English language publications were retrieved that provided quantitative statistical analysis of outcomes on blood pressure and immune function.

Results: The 7 meta-analyses that were included in this umbrella review reported significant positive benefits for reducing systolic and diastolic blood pressure in hypertensive adults by 2.2 to 5.4 mm Hg and 2.7 to 3.1 mm Hg, respectively, reducing diastolic blood pressure in pregnant women with gestational hypertension by 4.9 mm Hg, and reducing the length of stay in the hospital for surgical patients; in addition, 2 of the 3 meta-analyses indicated a 40% reduction in the incidence of hospital-acquired infections. However, these positive results should be considered with caution because statistically significant heterogeneity was observed in 5 of the 7 meta-analyses.

Conclusions: Some evidence appears to support the benefit of L-arginine supplementation for reducing systolic and diastolic blood pressure in hypertensive adults and reducing the incidence of hospital-acquired infections and the length of stay in the hospital for surgical patients. Given the limitations of the included studies, interpretations should be made with caution. (J Chiropr Med 2016;15:184-189)

Key Indexing Terms: *Arginine; Meta-analysis; Hypertension; Infection*

INTRODUCTION

L-Arginine is a semi-essential amino acid that is particularly rich in certain foods such as meats and nuts. L-Arginine is the substrate for the enzyme nitric oxide synthase (NOS), which is responsible for the production of nitric oxide. Nitric oxide produced in the vascular endothelium by endothelial NOS is responsible for smooth muscle cell relaxation and essential for reducing blood pressure. Any improvement in endothelial function will help in the prevention of cardiovascular disease.[1] L-Arginine is also used by the cells of the immune system where the enzyme inducible NOS produces nitric oxide for cell signaling or oxidative bactericidal actions.[2] Therefore, L-arginine could help reduce infection rates, especially in situations that compromise immune function such as surgery or critical illness.[3]

Many clinical trials have been carried out to evaluate the role of L-arginine in blood pressure regulation in both hypertensive and preeclampsia populations. However, the sample sizes for the majority of these trials were small, and the results were sometimes inconsistent and nonsignificant.[4] Likewise, clinical studies of L-arginine supplementation and surgical or hospital patients' infection rates and length of stay in the hospital have used small sample sizes, and the outcomes for some did not achieve statistical significance.[5] It has been stated that the efficacy of L-arginine at doses above standard dietary practices has not been established, and clinical studies have suffered from lack of statistical power, patient heterogeneity, and randomization failures.[3]

Given the inconsistency of the existing literature and the insufficient statistical power as a result of small sample sizes, a pooling of information from individual trials could

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provide a more precise and accurate estimate of L-arginine supplementation on blood pressure and immune function. To achieve this result, many investigators have turned to performing a powerful statistical method known as meta-analysis. Meta-analyses are fundamental for providing the highest level of evidence to best inform health care decision making.

The objective of this paper is to summarize the evidence from multiple research syntheses to examine the efficacy of L-arginine's role as a therapeutic agent. To accomplish this goal it was deemed necessary to conduct an umbrella review. An umbrella review provides a summary of existing research syntheses and an assessment of whether authors addressing similar review questions independently observe similar results and arrive at similar conclusions.[6]

METHODS

A systematic literature search of PubMed, the Cochrane Library, and Cumulative Index through Nursing and Allied Health Literature from January 1, 1980 through December 31, 2015 was conducted using the following search strategy: "(arginine) AND (meta-analysis OR systematic review)". Only English language publications were retrieved that provided quantitative statistical analysis of outcomes on blood pressure and immune function. Meta-analyses or systematic reviews that did not present study-specific summary data using a minimum of 4 randomized controlled trials were excluded.

For the published papers that were accepted into this review, the following information was abstracted and entered into an Excel spreadsheet: number of publications included in the meta-analysis, number of total participants, dose and method of L-arginine supplementation, pooled treatment effects for clinical endpoints such as systolic and diastolic blood pressure, relative rate for infection incidence, and length of hospital stay in days. Because this is a descriptive summary review of meta-analyses, no statistical analyses were performed.

Papers were also assessed for their disclosure of quality assessment, statistical heterogeneity (Cochran Q test and I^2 statistic), and publication bias (visual inspection of funnel plots and the Egger or Begg regression test).

RESULTS

The initial search strategy yielded 93 citations. Of these, 84 were excluded, and after further review, 2 more meta-analyses were excluded because they were both based on the statistical analysis of only 2 clinical trials (one investigated the use of L-arginine supplementation on clinical outcome for patients with acute myocardial infarctions, and the other investigated the use of L-arginine supplementation in prevention of necrotizing enterocolitis in premature infants).[7,8] The remaining 7 meta-analyses

were retrieved for inclusion in this umbrella review.[9-15] A flow chart of the selection process of the meta-analyses is shown in Figure 1, and Table 1 provides the detailed analysis from the 7 meta-analyses reviewed.

In regard to quality assessment, all 7 meta-analyses performed such an assessment, with 2 meta-analyses excluding studies because of low quality.[11,14] Gui et al[11] excluded 1 study and Vidal-Casariego et al[14] excluded 5 studies from their meta-analyses because of low scores on the Jadad quality assessment scale. Of the 7 meta-analyses that performed quality assessments, 3 used the Jadad quality assessment scale, 3 used a 0 to 5 quality assessment scale, and 1 used a 0 to 14 scale. All but 1 of the 7 meta-analyses did not state their results. On average, one-half of all the studies entered into these meta-analyses were rated as being of high quality. The high-quality studies in these meta-analyses are presented in Table 1.

The main findings in this umbrella review indicate that L-arginine supplementation significantly reduced systolic and diastolic blood pressure in a population of mostly hypertensive adults (hypertensive participants making up 72% of the population), but only diastolic blood pressure was significantly reduced in pregnant women. L-Arginine supplementation also significantly improved vascular endothelial function as measured by flow-mediated dilation (FMD). L-Arginine provided via enteral route to surgical patients reduced infection rates and the length of stay in the hospital, but infection rates were not significantly reduced in patients undergoing surgery for head and neck cancer. Hospital patients taking intravenous L-arginine therapy exhibited significant elevations in their CD4 T-cell counts (increased T-helper cell development). For all 7 meta-analyses, the outcomes were obtained from a fixed-effects model, except when there was significant heterogeneity, and then a random-effects model was used.

All 7 meta-analyses performed heterogeneity testing, with all 7 using the Cochran Q test and 6 of the 7 using the I^2 statistic. The P values for the Cochran Q test and the I^2 statistic percentages are shown in Table 1. Significant heterogeneity was observed in the overall results for systolic blood pressure in both the adult population and the pregnant women population, FMD, length of stay for surgical patients, and CD4 count in hospital patients.

Four of the 7 meta-analyses tested for publication bias using visual assessments of the funnel plots for asymmetry and 5 performed either the Egger or Begg regression test, neither of which found statistically significant publication bias in any of the meta-analyses assessed. The P values for both the Egger and Begg regression tests are shown in Table 1.

DISCUSSION

For hypertensive adults, L-arginine supplementation significantly reduces both systolic and diastolic blood