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

Marc P. McRae, MSc, DC, FACN, DACBN

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

Department of Basic Science, National University of Health Sciences, Lombard, IL.

Corresponding author: National University of Health Sciences, 200 E. Roosevelt Rd., Lombard, IL 60148. Tel.: +1 63 889 6592. (e-mail: *mmcrae@nuhs.edu*).

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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

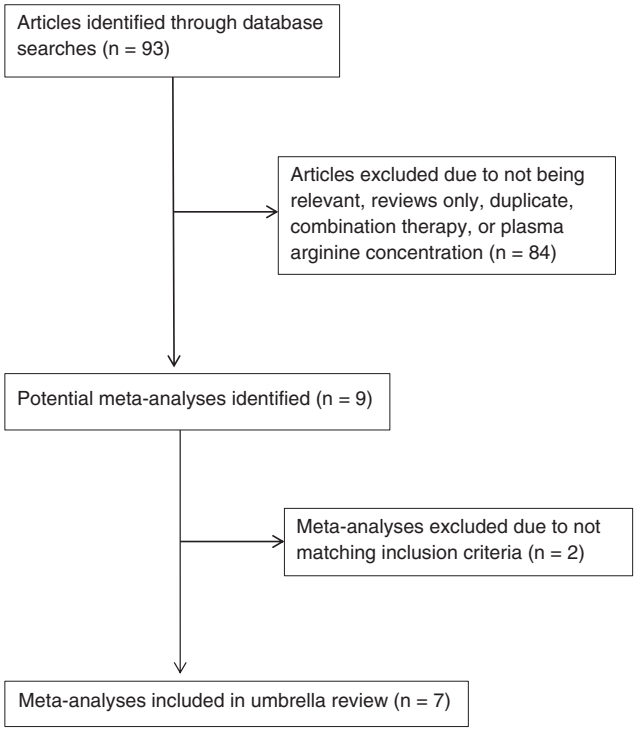

Fig 1. *Flow chart of meta-analysis selection.*

pressure by 2.2 to 5.4 mm Hg and 2.7 to 3.1 mm Hg, respectively. These results are just slightly better compared with the findings in the vitamin C, vitamin D, and magnesium supplementation meta-analyses, which indicated reductions in systolic and diastolic blood pressure of 3 to 4 mm Hg and 1.5 to 3 mm Hg, respectively.[16-18] Extrapolating from a review based on more than 600 000 participants, these modest changes in blood pressure are clinically significant because a 5–mm Hg reduction in systolic blood pressure is associated with a 14% reduction in stroke risk and a 9% reduction in coronary heart disease risk.[19] The overall reduction in systolic and diastolic blood pressure presented in this umbrella review could have been better because 4 of the 11 studies in the meta-analysis by Dong et al[9] used normotensive adults in whom there could have been less room for improvement. Although no publication bias was observed in this meta-analysis, significant heterogeneity was found with the systolic blood pressure results. Possible reasons for finding significant heterogeneity beyond the obvious difference in hypertensive versus normotensive populations include differences in diets, medications, exercise prescription, and duration of the trials. Also, the participants in the different trials possessed different comorbidities such as diabetes, hypercholesterolemia, coronary artery disease, and gestational hypertension. Regarding mechanism of action, L-arginine is the substrate for the enzyme endothelial NOS, which is found inside vascular endothelial cells and is responsible for the production of nitric oxide, which immediately leaves the endothelial cells to initiate vascular smooth muscle cell relaxation.

This improvement in endothelial function with L-arginine supplementation can be measured by using FMD. FMD represents the ability of the brachial artery to dilate in response to ischemia-induced hyperemia. The dilation is dependent on the production of nitric oxide by the vascular endothelium. The 1 meta-analysis in this umbrella review on L-arginine's effects on FMD reported significant beneficial results, but, again, these results are hampered by the finding of significant heterogeneity.

In both meta-analyses on pregnant women with gestational hypertension, L-arginine supplementation produced significant reductions in diastolic blood pressure but nonsignificant reductions in systolic blood pressure. No publication bias was observed, but 1 of the 2 meta-analyses found significant heterogeneity with systolic blood pressure. This observed significant heterogeneity may be accounted for by the different routes of L-arginine supplementation (oral vs intravenous) as well as the different doses used by the various studies. In regard to mechanism of action, L-arginine concentrations have been demonstrated to be significantly reduced in women with gestational hypertension or preeclampsia.[20] Significantly reduced levels of circulating nitric oxide have also been detected. It has been observed that in pregnant women with preeclampsia, the levels of superoxide increase, and this reacts rapidly with nitric oxide, resulting in a significant reduction in circulating nitric oxide and a subsequent increase in blood pressure.[21] Therefore, increasing the production of nitric oxide through L-arginine supplementation can overcome the oxidative effects of superoxide production and significantly reduce blood pressure.

For surgical or hospital patients, 2 of the 3 meta-analyses found L-arginine supplementation significantly reduced the relative rate of acquiring a hospital-based infection by 40%, and infectious complications included pneumonia, abdominal abscess, septic shock, fasciitis, and urinary tract infections. No publication bias was observed, but significant heterogeneity was observed in 1 of the 3 meta-analyses. L-Arginine is used by immune cells to produce nitric oxide (via inducible NOS) to enhance cell-mediated immune function through modulation of cytokine production as well as lymphocyte proliferation and differentiation.[2] This effect can be found in the meta-analysis on hospital patients who had a significant increase in CD4 count, but, again, this result is tempered by the observation of significant heterogeneity.

The 2 meta-analyses on surgical patients and patients with head and neck cancer reported a significant decrease in length of stay in the hospital; however, the larger of the 2 meta-analyses noted observation of statistically significant heterogeneity. The significant heterogeneity observed in

Table 1. *Summary of the 7 Meta-analyses That Qualified for This Umbrella Review on L-Arginine*

Meta-analysis Authors and Date	No. of Studies in Meta-analysis	No. of Participants in Meta-analysis	Average L-Arginine Dose and Duration	Main Findings of Meta-analysis	Quality Assessment Scale and Outcome	*Q* Test *P* Value	I^2 Statistic	Egger or Begg Test *P* Value
Dong et al. 2011[9]	11	387 adults (72% with hypertension)	11 g/d oral for 5 wk	SBP ↓ 5.4 mm Hg, *P* = .001 DBP ↓ 2.7 mm Hg, *P* < .001	Yes (Jadad) 3/11 high 2/11 low	SBP *P* = .000 DBP *P* = .115	SBP 73% DBP 34%	SBP *P* > .3 DBP *P* > .3
Zhu et al. 2013[10]	5	296 pregnant women	8 g/d oral or 25 g/d IV for 10 d	SBP ↓ 2.2 mm Hg, *P* = .19 DBP ↓ 3.1 mm Hg, *P* = .004	Yes 2/5 high	SBP *P* = .64 DBP *P* = .80	SBP 0% DBP 0%	SBP *P* = .63 DBP *P* = .47
Gui et al. 2014[11]	4	204 pregnant women	8 g/d oral or 25 g/d IV for 10 d	SBP ↓ 3.2 mm Hg, *P* = .19 DBP ↓ 4.9 mm Hg, *P* < .0001	Yes (Jadad) 2/4 high Excluded 1 study for low quality	SBP *P* = .05 DBP *P* = .31	SBP 61% DBP 16%	NR
Bai et al. 2009[12]	13	493 adults	10 g/d oral for 18 d	FMD = 1.98, *P* = .01	Yes Results not shown	*P* < .0001	98%	*P* = .49
Drover et al. 2011[13]	28	2780 surgical patients	NR	Infection RR = 0.59, *P* < .0001 LOS ↓ 2.4 days, *P* < .0001	Yes Average score was 8.2/14	Infection *P* = .11 LOS *P* < .0001	Infection 26% LOS 87%	Infection *P* = .70 LOS *P* = .22
Vidal-Casariego et al. 2014[14]	5	348 patients with head and neck cancer	11.7 g/L enteral administration for 7.5 d	Surgical site infection OR = 1.04, *P* = .93 Other infections OR = 0.79, *P* = .37 Postoperative fistulas OR = 0.36, *P* = .04 LOS ↓ 6.8 d, *P* = .02	Yes (Jadad) 3/5 high Excluded 5 studies for low quality	Surgical site infection *P* = .81 Other infections *P* = .10 Postoperative fistulas *P* = .27 LOS *P* = .49	NR	*P* = .98
Kang et al. 2014[15]	6	168 hospital patients	16 g/d IV for 16 d	Infection OR = 0.40, *P* = .04 Albumin ↑ 0.10 g/dL, *P* = .0003 CD4 count ↑ 5.03, *P* = .01	Yes 8/11 high	Infection *P* = .94 Albumin *P* = .15 CD4 count *P* = .03	Infection 0% Albumin 37% CD4 count 59%	NS Symmetrical funnel plots

DBP, diastolic blood pressure; *FMD*, flow-mediated dilation; *IV*, intravenous; *LOS*, length of stay in hospital; *NR*, not reported; *NS*, not significant; *OR*, odds ratio; *RR*, relative risk; *SBP*, systolic blood pressure.

this meta-analysis could be explained by the fact that the 28 studies included in this meta-analysis were composed of hospital patients who were certainly not a homogeneous group. Publication bias was not observed in either of these 2 meta-analyses. With respect to mechanism of action, L-arginine can promote protein synthesis and accelerate wound healing.[22] L-Arginine can hasten the repair of damaged tissues and therefore reduce healing time via 2 mechanisms. First, arginine is a precursor for proline synthesis, which is important for collagen synthesis and wound healing, and second, L-arginine is also a precursor for polyamine synthesis, which is known to promote cell growth, proliferation, and differentiation.[23,24] L-Arginine also acts as a secretagogue because it stimulates the release of several anabolic hormones, such as insulin, growth hormone, and insulin-like growth factor 1.[25]

Five of the 7 meta-analyses addressed the adverse effects that might arise from supplemental L-arginine. Four of these 5 meta-analyses documented adverse side effects related to complaints of diarrhea and nausea, but in total, this only

amounted to 7 of 33 individual papers registering complaints. This result is in keeping with the belief that daily dosing of more than 9 g/d of L-arginine can be associated with gastrointestinal discomfort, nausea, and diarrhea for certain patients.[26]

Limitations

One limitation of this umbrella review is that only 3 indexing systems were searched, and, thus, it is possible that some meta-analyses were not identified. Another limitation is that only 1 author performed the search and selection of the meta-analyses included. Finally, as in all literature reviews, the quality of this umbrella review is directly related to the quality of the included meta-analyses.

Conclusions

The meta-analyses in this umbrella review indicate that use of L-arginine provides significant positive benefits for reducing systolic and diastolic blood pressure in hypertensive adults, reducing diastolic blood pressure in pregnant women with gestational hypertension, and reducing the length of time in the hospital for surgical patients; 2 of the 3 meta-analyses reported a 40% reduction in the incidence of hospital-acquired infections. However, these results must be applied with caution because statistically significant heterogeneity was observed in 5 of the 7 meta-analyses, and this weakens the inferences that can be made from these results.

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No funding sources or conflicts of interest were reported for this study.

Contributorship Information

Concept development (provided idea for the research): M.P.M.
Design (planned the methods to generate the results): M.P.M.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): M.P.M.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): M.P.M.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): M.P.M.
Literature search (performed the literature search): M.P.M.
Writing (responsible for writing a substantive part of the manuscript): M.P.M.
Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): M.P.M.

Practical Applications

- The findings of this review show support for the use of L-arginine supplementation for reducing blood pressure in hypertensive patients, as well as reducing the incidence of infections and length of stay in hospital.

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