The do's and don'ts of arginine supplementation

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Abstract

In the last three decades the nutritional and pharmacologic effects of arginine have been the subject of intense investigation. Taking into consideration the many benefits that have been demonstrated from arginine supplementation, the question remains: "Can we afford not to supplement with this immuno-nutrient". The potential life-saving cardiovascular effects of arginine in both acute and chronic arginine supplementation has the ability to revolutionise the management of vascular disease, yet much more research must be done in this area. In addition, the proposed benefits of such supplementation in the sepsis model, makes arginine a very attractive model for decreasing the mortality statistics of this worldwide disease process. However, owing to the fact that arginine is a precursor for nitric oxide synthesis, the effects of which are potentially detrimental in the septic patient, further research is warranted in this field to determine the suitability of this agent in patient management.

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Introduction

Nutritional therapy (in critical care) has generally been designed to meet the body's nutritional needs for energy, protein and micronutrients. More recently, specialised nutritional supplements have been added to the standard enteral feeds to modulate the immune system. These nutrient supplements have been combined to form speciality enteral products referred to as immune-enhancing diets (IED). The body of literature supporting the use of IED has grown substantially in recent years and in 2001 consensus guidelines were developed by a panel of leading experts in the field.

There are a large number of these immuno-nutrients, each, or collectively, providing their own range of benefits for the critically ill patient. These include, but are not limited to, arginine, glutamine, omega fatty acids and selenium. Each of these compounds can be administered individually or combined with other nutritional support products.

Pharmaconutrition is a term that was coined by Heyland and colleagues[1] proposing that the administration of immuno-nutrients be dissociated from the provision of enteral nutrition so that their full dose can be delivered and their therapeutic effects evaluated appropriately without being influenced by the disruption of feeding regimens. This concept is important when one considers that the combination of immuno-nutrients and feeds results in sub-therapeutic doses of the former being administered due to interruptions of feeding. These interruptions are usually due to digestive intolerance, mechanical complications with feeding tubes, airway management, diagnostic procedures or infusion pump inaccuracies.

Arginine

Arginine is a non-essential amino-acid that is thought to become conditionally essential during growth and recovery following injury. It acts as a precursor of nitric oxide, polyamines (important in lymphocyte maturation) and nucleotides.

In the last three decades the nutritional and pharmacologic effects of arginine have been the subject of numerous studies.[2] Following initial work demonstrating that large doses of supplemental arginine possess immune-enhancing, wound-healing, and anti-tumour properties, there has been increased effort in defining possible clinical uses for arginine.[3]

Furthermore, the demonstration that arginine is the unique substrate for nitric oxide synthesis stimulated further research in this area, with particular focus on traumatic/haemorrhagic shock and sepsis.[4] However, nitric oxide has been implicated as one of the aetiological factors responsible for systemic vasodilation during the systemic inflammatory response syndrome (SIRS) and therefore the use of arginine in this situation could potentially worsen patient outcome.

Arginine metabolism

Arginine is a dibasic amino acid. It is considered to be a dietary conditionally dispensable amino acid. The average daily dietary consumption of arginine is 5–6 g. Under normal conditions, endogenous daily production of 15–20 g occurs via the citrulline intestinal-renal axis.[2]

A large proportion of arginine is used in protein synthesis, approximately 5% in urea synthesis, and a small portion (< 5%) is utilised by the nitric oxide synthase (NOS) enzyme system for

conversion to nitric oxide (NO). The intestinal absorption of arginine occurs via a transport system shared with lysine, ornithine, and cysteine. Arginine, ornithine, and lysine also share a common uptake and transport system in the brain, leukocytes, erythrocytes, fibroblasts, and leukocytes.[2]

The quantities of arginine produced normally are sufficient to maintain muscle and connective tissue mass. However, endogenous synthesis of arginine is insufficient to meet the heightened demands that increased protein turnover requires during periods of stress, such as critical illness. In such situations, arginine becomes indispensable for optimal growth and maintenance of positive nitrogen balance.[2]

Arginine also plays a key role within the urea cycle, the major pathway for ammonia detoxification. Arginase, the enzyme responsible for the catabolism of arginine in the urea cycle, has two distinct isoenzymes encoded by separate genes. **Type I arginase**, a cytosolic enzyme, is highly expressed in the liver as a component of the urea cycle, and is also present in wound-derived fibroblasts. **Type II arginase** is a mitochondrial enzyme expressed at lower levels in the kidneys, brain, small intestine, mammary glands, and macrophages. Any condition that increases demand for ammonia detoxification is likely to increase arginine requirements (Figure 1).[2]

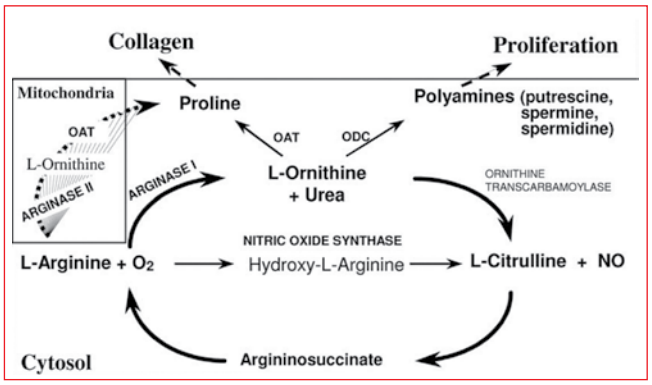

Figure 1: Metabolic pathways of arginine (OAT: ODC: NO:). *OAT,* ornithine aminotransgerase; *ODC,* ornithine decarboxylase; *No,* nitric oxide

This important pathway has been shown to be present in many tissues and cells including endothelium, brain, inflammatory cells (lymphocytes, macrophages, neutrophils, and mast cells), platelets, and hepatocytes. In addition to its role in vasodilatation, NO is a reputed neurotransmitter and cytotoxic effector molecule. NO is formed by oxidation of one of the two identical terminal guanidine groups of L-arginine, by NOS, a dioxygenase for which there are at least two identified isoforms. Both isoforms of NOS have been identified as flavoproteins, each containing flavine adenine dinucleotide and flavine adenine mononucleotide, and both are inhibited by diphenyleneiodonium, a flavoprotein inhibitor. Neuronal and endothelial NOS are expressed constitutively and are activated by Ca^{2+} /calmodulin. Inducible NOS is calcium independent and is expressed in response to inflammatory cytokines and endotoxins including interleukin-1, tumor necrosis factor-α, γ-interferon, and lipopolysaccharide.[2]

A third degradative pathway for arginine only recently has been described in mammalian tissues. This involves the decarboxylation of arginine to agmatine. The importance of this pathway in mammalian brain and other tissues is just beginning to be elucidated.[5]

Clinical Pharmacology of Arginine Supplementation

L-arginine is the precursor for the endogenous synthesis of NO due to the activity of NOS, which releases L-citrulline as a byproduct.[6,7,8] Although only a minor portion of L-arginine is metabolised via this pathway in vivo, it has attracted much interest in recent years because of the prominent role that NO plays in vascular physiology and pathophysiology. NO generated from L-arginine is a highly reactive radical gas and an important messenger molecule. At low concentrations like those produced by constitutive endothelial NOS (ecNOS) in the vasculature in vivo, NO acts as a paracrine-signaling molecule, mediating vasodilation,[9] inhibition of platelet activation,[10] inhibition of monocyte and leukocyte adhesion,[11] and inhibition of smooth muscle cell proliferation[12] and controlling vascular oxidative stress and the expression of redox-regulated genes.[13]

In certain animal models and in some human diseases, the biological functions of endothelium-derived NO are impaired, leading to dysregulation of endothelial control of vascular tone and blood flow. Such models include hypercholesterolaemic rabbits, rat models of hypertension, and hyperlipidaemic monkeys.[14] The mechanisms of this phenomenon are probably multi-factorial, including reduced NO elaboration by NOS, increased oxidative inactivation of NO, and enhanced formation of vasoconstrictor mediators like endothelin-1 and thromboxane A2.[14]

What then is the role of L-arginine in this setting?

NOS is inhibited by L-arginine analogs that are substituted at the guanidino nitrogen atom, like *N*G-monomethyl- L-arginine or *N*G-nitro-L-arginine.[15] Inhibitory action of these molecules is overcome by excess L-arginine,[15] indicating that there is competition for enzyme binding between L-arginine and its inhibitory analogs. Reduced activity of endothelial cell NOS was also shown to occur in the presence of low-density lipoprotein cholesterol; again, this effect can be overcome by excess L-arginine.[16] Although the mechanism of this latter phenomenon has not yet been fully elucidated, these data demonstrate that, under certain conditions, L-arginine availability regulates endothelial cell NOS activity.

Soon after these first animal experiments had demonstrated a beneficial effect of L-arginine on endothelial function, it was shown that local intracoronary infusion of L-arginine normalised coronary vasomotor responses to acetylcholine in hypercholesterolaemic humans.[17] A similar observation was also made upon systemic (intravenous) infusion of L-arginine in hypercholesterolaemic subjects, in whom endothelium-dependent forearm vasodilation was improved.[18] These are important findings, because endothelial dysfunction precedes angiographically visible atherosclerotic lesions in large coronary arteries.[19] Evidence from prospective clinical trials suggests that endothelial dysfunction is a predictor of future coronary events and therefore, reversal of endothelial dysfunction by L-arginine in vivo may suggest that this amino acid exerts anti-atherosclerotic effects in humans.[14]

Table I: Diseases in which L-arginine has been demonstrated to improve clinical end points of cardiovascular disease

Disease	L-arginine dose [a]	Effect
Peripheral Arterial Disease	3 x 8g/d iv 30g iv	Increased Walking distance[20] Increased Nutritive Muscle Blood Flow[21]
Coronary Artery Disease	3 x 3 g/d iv 3 x 2 g/d iv	Decreased Angina Symptom Score[22] Increased Exercise Capacity[23]
Congestive Heart Failure	5.6–12.6 g/d po	Increased Exercise Capacity[24]
Raynaud Syndrome	8.5 mg/min ia	Decreased Vasospasm Attacks[25]

'a – Routes of administration – iv = intravenously, po = orally, ia = intra-arterially

In addition to coronary artery disease, a number of studies have shown that oral L-arginine supplementation improves symptoms of certain vascular diseases as well (Table I).[14]

Although there is a bulk of evidence that supplementation with L-arginine—via the intra-arterial, intravenous, or oral route—improves endothelial dysfunction in hypercholesterolaemia and atherosclerosis, endothelial dysfunction in other cardiovascular diseases (like hypertension) was not shown to be consistently improved by L-arginine administration. Therefore, while there is great promise for this immune-nutrient is the treatment of vascular diseases, it is certainly not the panacea that the world seeks.

Arginine in sepsis

Sepsis is a major complication of an acute infection, triggered by a systemic inflammatory reaction. It is characterised by a reduction in plasma and tissue arginine levels compared with healthy individuals or nonseptic critically ill patients.[26,27,28] In addition, plasma amino acid levels are in general lower during sepsis, which is partly related to starvation due to limited nutritional protein supply, as well as to increased amino acid clearance[27] through gluconeogenesis, oxidation for energy supply, and protein synthesis in especially the liver and immune cells. This negative amino acid balance appears not to be compensated for by the excessive protein catabolism (protein breakdown is increased by 50% in septic patients) that occurs.

Recent evidence suggests that arginine metabolism in sepsis is disturbed in various aspects, probably related to the severity of the inflammatory response and induced by inflammatory mediators. In sepsis, the endogenous synthesis of arginine from the amino acid citrulline, is reduced to one third of the normal level.[28]

The rationale for arginine deficiency in sepsis is mainly based on the reduced arginine levels in sepsis that reflect the specific changes in arginine metabolism, with functional consequences regarding endothelial dysfunction, severe catabolism, impaired wound healing, and worse outcome. However, the direct effects of cytokines and hormones must also be considered in these pathophysiological processes as other amino acids can also be present in inadequate amounts.[29]

Only a few studies have investigated the effects of arginine supplementation in patients with sepsis. This exogenous arginine supplementation in sepsis shows controversial results with only limited data in humans and varying results in animal models of sepsis.

Since the severity of sepsis varies, and the route, timing, and dose of arginine differ between studies, it is difficult to draw a definitive conclusion for the effect of exogenous arginine supplementation in sepsis, based on these studies.

Although studies on arginine supplementation in septic patients are scarce, major risks of exogenous arginine are ascribed to the suggested increase in NO synthesis. Stimulated NO production is related to reduced blood pressure and is suggested to impair cardiac contractility, induce liver damage, and increase vascular permeability and bacterial translocation from the intestine. In addition, oxidative stress (through production of peroxynitrite- a harmful metabolite formed from NO and superoxide that nitrates the tyrosine residues in proteins to nitrotyrosine) and mitochondrial dysfunction are considered further risk factors of increased NO and, therefore, indirect results of exogenous arginine supply.

While enhanced NO production in sepsis is suggested to be related to the detrimental effects of hemodynamic instability and enhanced oxidative stress, potential mechanisms for beneficial effects of exogenous arginine supplementation in sepsis must also be considered. These include enhanced (protein) metabolism, improved (micro) circulation and organ function, effects on immune function and antibacterial effects, improved gut function, and an antioxidant role of arginine.

Taking these potential benefits into consideration and the fact that *Luiking et al*[30] have demonstrated that arginine can be given to septic patients without major effects on haemodynamics, more studies need to be done to determine the effects of arginine supplementation on septic patients.

Should we be supplementing arginine?

The benefits and side-effects of arginine supplementation tend to be related to the extent to which it influences the production of NO via the NOS pathway. As with any medication, over administration leads to undesirable effects which potentially lead to problems in the patient. This effect is made more obvious in patients where physiological homeostatic mechanisms are already at breaking point (such as in sepsis) (Figure 2).[31]

Taking into consideration the many benefits that have been demonstrated from arginine supplementation, the question remains: "Can we afford not to supplement with this immuno-nutrient".

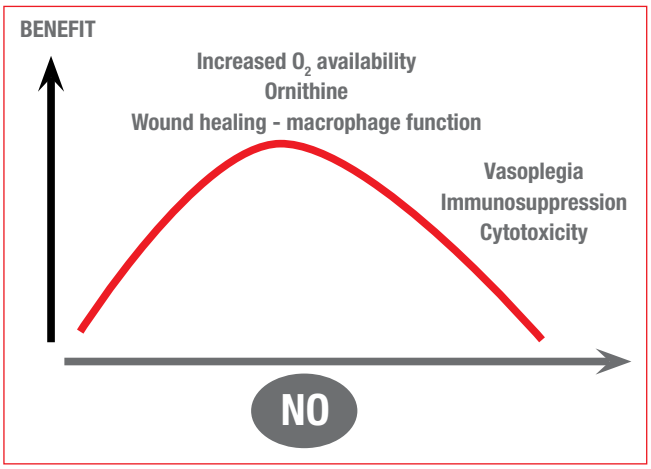

Figure 2: The beneficial and harmful effects of arginine supplementation. (*NO:* nitric oxide)

The potential life-saving cardiovascular effects of arginine in both acute and chronic arginine supplementation has the ability to revolutionise the management of vascular disease, yet much more research must be done in this area.

In addition, the proposed benefits of such supplementation in the sepsis model, makes arginine a very attractive model for decreasing the mortality statistics of this worldwide disease process. However, owing to the fact that arginine is a precursor for NO synthesis, the effects of which are potentially detrimental in the septic patient, further research is warranted in this field to determine the suitability of this agent in patient management.

Therefore, while both in-vitro and in-vivo work points towards arginine being a very useful immuno-nutrient in the management of both vascular diseases and sepsis, a lot more research must be done to determine not only the extent of the benefits of this therapy, but also the doses required to achieve these benefits. In addition safety data is lacking, especially with regards to the role of NO in the septic patient. The question remains: Will arginine supplementation lead to worsening of the inflammatory response in the septic patient?

In summary

The Do's – Keep abreast of the new research being done in the field of arginine supplementation and the potential benefits this therapy may provide.

The Don'ts – Be cautious and do not start your patient on supplemental arginine just yet. While there are potentially great therapeutic benefits in this treatment modality, its safety (especially in sepsis) is still to be consistently documented.

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