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RESEARCH ARTICLE

Assessing the efficacy of L-arginine and vitamin C supplementation in pediatric Long-COVID: a Randomized Controlled Trial

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ABSTRACT

Following acute SARS-CoV2 infection, both in pediatric and adult populations, lingering or new symptoms may arise, leading to a condition known as Long-COVID. Understanding the pathophysiological basis of this condition has enabled the identification of supportive therapeutic strategies. Endothelial damage and oxidative stress seem to play a dominant role in the pathogenesis of Long-COVID. These patients experience a relative deficiency of L-arginine, and supplementation of L-arginine may improve endothelial function by promoting the activity of nitric oxide synthase (NOS). Additionally, vitamin C supplementation could reduce oxidative stress caused by the pro-inflammatory state typical of this condition. In this randomized and controlled trial, we assess the therapeutic effects of the combination of L-arginine and vitamin C in a pediatric population diagnosed with Long-COVID. The primary outcome was to evaluate the improvement in quality of life and changes in scores on the Borg scale, chosen as an indirect indicator of respiratory function. Thirty-six patients were recruited and divided into 3 treatment arms. Results showed improvement in the Borg scale at 30 ($p < 0.01$) and in quality of life ($p < 0.001$) among treated *vs*. untreated patients. Therefore, this supplementation may be considered in the treatment of Long-COVID in the pediatric age group.

HIGHLIGHTS BOX

What is already known about this topic? The use of L-arginine in Long-COVID in adulthood is supported by various scientific evidence, there are few references regarding its use and effectiveness in pediatric age. **What does this article add to our knowledge?** Arginine supplementation in the pediatric age improves the symptoms of Long- COVID, raising the quality of life of children. The use could be extended to post-viral syndrome potentially caused by other viruses. **How does this study impact current management guidelines?** There are no guidelines on the treatment of Long-COVID in the pediatric age. However, the use of L-arginine and vitamin C is an effective and safe strategy in its management, in particular improving asthenia and fatigue, allowing the recovery of psychophysical and relational performance.

KEY WORDS

Long-COVID; L-arginine; children; therapy; vitamin C.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is characterized by an acute infection and a set of symptoms and comorbidities that can remain and persist after the end of the acute phase identifying a condition called Long-COVID. Different organizations have provided similar but different diagnostic parameters to diagnose Long-COVID. The World Health Organization (WHO) suggested a clinical definition for Long-COVID-19, indicating it typically manifests around three months after the onset of COVID-19. The symptoms should endure for at least two months and cannot be attributed to an alternative diagnosis (1).

The prevalence of Long-COVID in the pediatric age, based on the data available in the literature, is variable and depends on a series of risk factors (third childhood and transition age, female sex, history of allergic diseases, other chronic underlying disease, patients with severe symptoms in the acute phase of COVID-19) (2). The most reported symptom is nasal congestion (17%), followed by headache (15%), fatigue (13%), loss of appetite (10%), insomnia (9%), cough (8%), abdominal pain (6%), confusion and lack of concentration (5.2%), skin rashes (4.9%). Fatigue, insomnia, lack of concentration and headaches are the symptoms that have the greatest impact on the daily lives of enrolled patients. Headaches and insomnia lasted longer: the first up to 4-6 months after the infection, the second up to a year later. Approximately one in ten children has multisystem involvement, presenting two or more symptoms simultaneously (3).

The mechanisms through which Long-COVID is established are not yet clear; however, various pathophysiological mechanisms involving the virus have been hypothesized (4). First, direct tissue damage caused by the virus in acute infection could contribute to developing long-term complications. The cellular entry gate for the virus angiotensin-converting enzyme 2 (ACE2) is distributed in many tissues of our body (epithelial cells, nasal goblet cells, gastrointestinal epithelial cells, pancreatic β cells, and renal podocytes), suggesting the involvement of different tissues and organs in the acute phase and the possible outcomes of the infection. In addition to the long-term consequences of cellular damage created by primary infection, there are other mechanisms (5):

- endothelial damage: endothelial cells (ECs) express ACE2, SARS-CoV-2 can directly infect and reproduce within ECs (6-8). Moreover, the simultaneous release of inflammatory cytokines like IL-6, IL-1, and TNF can activate ECs, exacerbating the situation. The activated complement system can also cause harm to ECs (9-11);
- dysregulation of the immune system due to the finding of autoreactive T cells in patients infected with COVID-19, like what is found in subjects with autoimmune diseases;
- PCR-positive persistent low-level detection of SARS-CoV-2 infection in patient with symptomatic Long-COVID (12).

Several nutraceuticals have been used to improve the clinical status of Long-COVID patients (13). Among these, L-arginine has proven to be particularly effective. This molecule plays a key role in the regulation of respiratory functions, the immune system and endothelial function. Reduced levels of L-arginine and the resulting dysfunction of nitric oxide synthase (NOS) play a direct role in various respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchopulmonary dysplasia, and pulmonary hypertension (14).

Arginine's impact extends to aspects of cellular defense function, likely through the mediation of nitric oxyde (NO) formation by cNOS (15). These beneficial effects of arginine on cellular defense function have prompted its incorporation into contemporary immune-enhancing formulas aimed at lowering infectious morbidity and mortality among critically ill and immunocompromised patients.

L-arginine can be a substrate of the NOS, producing NO with a beneficial effect on the vascular endothelium or be metabolized by the arginase enzyme into ornithine, a step associated with endothelial and immune dysfunction.

During acute SARS-CoV2 infection, the balance between the activity of these two enzymes is altered and the enzymatic activity of arginase increases, leading to a reduction in the levels of available plasma L-arginine, a lower activity of the nitric oxide synthase enzyme and lower NO production (**Figure 1**) (16). In fact, reduced levels of plasma L-arginine and increased arginase activity were found in adult patients with Long-COVID and pediatric

patients with Multisystem Inflammatory Syndrome (MIS-C) compared to healthy controls (17). Alterations of this metabolic pathway are associated with increased dysregulation of the immune system, endothelial dysfunction, inflammation, thrombosis (17).

Unlike most animals, humans cannot produce vitamin C internally, so it is necessary to obtain it through diet. The recommended daily intake of vitamin C is typically 75 mg for women and 90 mg for men. Ascorbic acid serves as a cofactor for various enzymes (such as dopamine B-monooxygenase, prolyl 4-hydroxylase, and lysyl hydroxylase) and plays a fundamental role in protecting cellular components from damage caused by free radicals produced during metabolism (18).

Similarly, recent clinical trials have highlighted the beneficial effect of vitamin C in improving oxidative imbalance and vascular remodeling resulting from endothelial dysfunction and the reduction of capillary permeability, a concept that plays an important role in infectious diseases, including COVID-19 (19). Therefore, administering vitamin C could be effective in speeding up recovery following the acute phase of the infection (20).

A study conducted by Tosato M and colleagues on 46 adults (median age 51, 65% women) found that after 28 days of receiving L-arginine plus vitamin C, supplementation improved walking performance, muscle strength, and reduced fatigue in adults with Long COVID (21).

Another interesting finding from a study on an adult population comes from a survey conducted by Izzo *et al.* with 1,390 participants. It revealed that patients in the L-Arginine + vitamin C treatment group had significantly lower scores for effort perception ($p < 0.0001$) compared to those who received the multivitamin combination (22). Based on these observations, a possible strategy for improving the symptoms of Long-COVID, even in pediatric age, is the oral supplementation of L-arginine combined with vitamin C.

The objective of this study was to evaluate whether combined therapy with L-Arginine and liposomal vitamin C (Bioarginina C, Farmaceutici Damor S.p.A., Italy) in pediatric patients with previous SARS-CoV2 infection and symptoms attributable to Long-COVID can determine a gain in terms of remission of symptoms and improved quality of life.

MATERIALS AND METHODS

Within our specialized pediatric pulmonology unit, we have established a clinic dedicated to children with a previous SARS-CoV-2 infection. We enrolled all patients who, during the outpatient evaluation (from March to October 2022), were diagnosed with Long-Covid and met the inclusion criteria (listed below). After obtaining approval from the ethics committee and obtaining informed consent, the study involved the enrollment of patients who met the following inclusion criteria: age

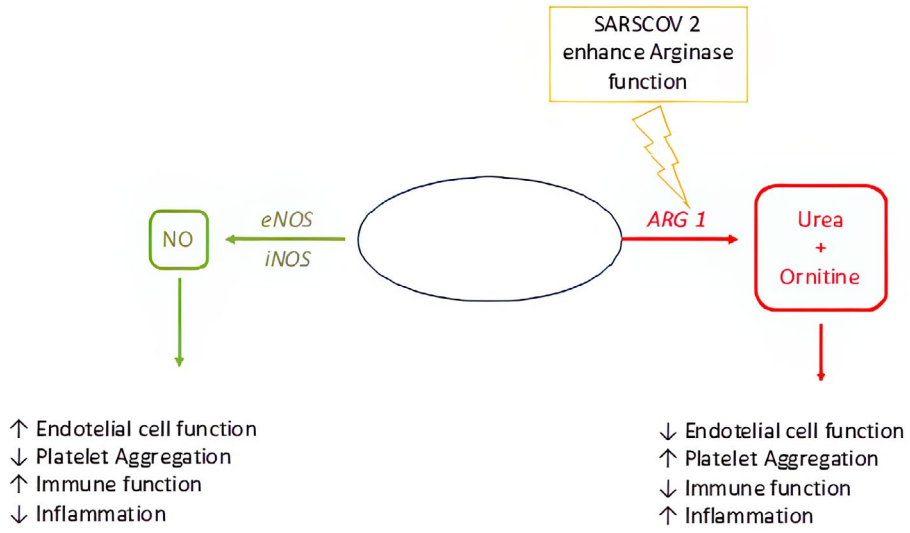

***Figure 1**. Metabolic pathways of L-arginine.*

between 5 and 14 years; previous SARS-CoV2 infection ascertained by nasopharyngeal swab; negative to SARS-CoV2 on nasopharyngeal swab for at least 3 weeks (however, for all patients, enrollment occurred at least 60 days after the primary infection); presence of symptoms, attributable to Long-COVID absent in the period preceding the SARS-CoV2 infection (asthenia, reduced exercise tolerance, respiratory symptoms, abdominal pain, headache).

The study includes 3 assessments, respectively at enrollment in the study (T0), after 30 days (T30) and after 60 days (T60). The patients with the previously described criteria and symptoms attributable to Long-COVID were enrolled, randomized into three study arms:

1) treatment with Bioarginine C, 2 vials per day for 30 days, starting from T0;
2) treatment with Bioarginine C, 2 vials per day for 30 days starting from T30;
3) control group untreated and observed for 60 days.

At T0 a clinical check-up of the child was carried out with the:

– administration of the Long-COVID follow-up questionnaire (in which for each symptom it is necessary to express a degree of severity ranging from 0, absence of the symptom, to 3, maximum degree of severity of the symptom);
– Borg cr10 scale score assigned by the caregiver after asking, including during telephone interviews, the same questions that explored the child's effort in performing daily activities compared to the period before the onset of symptoms, such as 'climbing a flight of stairs', 'playing with peers', and 'walking with the family';
– COVID-related psychological questionnaires on quality of life for specific age of the patient filled in by the doctor following instructions from the parent (Kid- & Kiddo-KINDL) (23, 24). The KINDL is a versatile tool designed to assess Health-Related Quality of Life in children and adolescents aged 3 years and above. Comprising 24 items, it is a concise, methodologically appropriate, and psychometrically reliable measure. This instrument has been translated into multiple languages and extensively utilized in both German and international studies. Norm values are established using representative data from the German National Health Interview and Examination Survey for Children and Adolescents (KiGGS).

None of the enrolled patients took any other medications during the observation period. Some received bronchodilator therapy during the acute infection.

These questionnaires were repeated, via telephone, by the same interviewer, 30 and 60 days after enrollment in the study.

Based on the data obtained from the analysis of the results of completing the questionnaires and from the assignment of a score on the Borg scale; we carried out a statistical analysis within each study arm at the different observation times (T0, T30 and T60) and between the three different study arms at the same observation time.

RESULTS

The study enrolled 36 children, with 12 patients for each of the three arms. The majority of the 36 patients

Table 1. *Enrolled patient features.*

	L-arginine + vitamin C	No treatment
No.	24	12
Median age	9.69	7.8
Female sex	18	6
Hospitalization for COVID-19	1	0

Table 2. *Sum of the severity scores obtained for each symptom within the different groups.*

	T0: GROUP 1	GROUP 2	GROUP 3
Hospitalization	1	0	0
Asthenia	10	12	6
Dyspnea	6	7	4
Chest tightness	4	9	4
Dizziness	3	3	3
Gastrointestinal symptom	6	2	4
Headache	8	8	6
Anosmia	0	0	0
Concentration difficulties	4	9	1
Sleep disorder	4	4	1
Cough	2	2	4
Rhinitis	4	0	4

Table 3. *Borg scale and quality of life (QoL) results in the 3 arms at different time points.*

		Improving of Borg scale	Quality of life questionnaires (kid- & kiddo-KINDL)
First study arms	After receiving 30 days of treatment (T0 *vs*. T30)	p < 0.030	
Second study arms	After receiving 30 days of treatment (T0 *vs*. T60)	p < 0.001	p < 0.001
Third study arms (no treatment)		Not significative	Not significative

involved in the study were female (M:F 1:2) and for 32 out of 36 cases inclusion in the study occurred more than 90 days after the primary SARS-CoV2 infection. Only one patient was hospitalized during the primary infection, the remainder developed a primary infection that passed paucisymptomatically. However, there were no substantial differences in terms of sex, age and hospitalization between patients treated with L-arginine+vitamin C compared to those not treated (**Table 1**).

In **Table 2**, we show, for each study group at T0 (enrollment), the sum of the severity of the different symptoms presented. From this perspective, the three samples exhibit a largely homogeneous distribution of the explored disorders.

In the internal analysis of the first study arm (**Table 3**), we found statistically significant differences regarding the improvement in the score attributed to the Borg scale between T0 and T30 (p < 0.030) and between T0 and T60 (p < 0.02). The internal analysis of the second arm of the study showed a statistically significant difference in the comparison between T0 and T60 regarding respectively the improvement of the scores assigned to the Borg scale (p < 0.001) and those attributed to the quality-of-life questionnaires (p < 0.001). No statistical significance was found regarding the internal analysis of the third study arm, *i.e.* those patients who did not receive any treatment and were observed for 60 days.

Regarding the comparison between different study arms at T30 (**Table 4**), a statistically significant difference emerged regarding the improvement in the Borg scale score between the first and second study arms (p < 0.004) and between the first and third study arms (p < 0.001); furthermore, at T30 there was a statistically significant difference in the improvement in quality of life between the first and second study arms (p < 0.001) and between the first and third study arms (p < 0.001). In the comparison between different study arms at T60 (**Table 4**), a statistically significant difference was highlighted regarding the improvement of the Borg scale score between the second and third study arms (p < 0.01) and between the first and third study arms (p < 0.01). Similarly, at T60, there was a statistically significant difference in the improvement in quality of life between arm 2 and arm 3 (p < 0.001) and between arm 1 and arm 3 (p < 0.001).

No adverse effects, even minimal ones, were reported in any patient treated.

DISCUSSION

The data extrapolated from the comparison between different study groups at the same timepoints show that an index susceptible to a rapid improvement (already after 30 days) following treatment with L-Arginine and liposomal vitamin C is the score on the Borg scale and

Table 4. *Borg scale and QoL results in the 3 arms at different time points.*

		Improving of Borg scale	Quality of life questionnaires (kid- & kiddo-KINDL)
T30	Study arms 1 *vs*. Study arms 2	p < 0.004	p < 0.001
	Study arms 1 *vs*. Study arms 3	p < 0.001	p < 0.001
T60	Study arms 2 *vs*. Study arms 3	p < 0.01	p < 0.001
	Study arms 1 *vs*. Study arms 3	p < 0.01	p < 0.001

that this improvement does not occur spontaneously in patients without being treated. While the scores obtained on the quality-of-life questionnaires show an observable and consistent improvement when compared between the different arms at T60. Data regarding the internal analysis of Groups 1 and 2 both show a statistically significant difference in the improvement of the Borg scale score between T0 and T60. Both groups received the combination treatment of L-arginine and vitamin C for 30 days. However, statistically significant improvements in Borg scale scores were not observed in the internal analysis of Group 3, the control group that did not receive any treatment. This comparison underscores that the improvement in treated patients was not solely due to potential spontaneous recovery within the sixty days, eliminating additional confounding factors given the homogeneity of the characteristics of the study groups.

This study confirms in the pediatric age the data already present in the literature for adults on the therapeutic effects of the association of L-arginine with vitamin C in patients with Long-COVID. Starting from the assumption of considering the dysfunction of endothelial cells (25, 26), as the main mechanism in the pathophysiology of Long-COVID, the result of damage to the vascular microcirculation established during the primary infection (given the abundant expression of ACE 2 receptors on the endothelial cell) which it is maintained once the primary infection phase has passed and can persist over time as highlighted by a clinical study in which the endothelial damage persisted even for a period longer than six months from the primary infection in the follow-up of patients affected by COVID19 compared to healthy controls (27). Furthermore, other studies have evaluated how the clinical manifestations related to Long-COVID, mainly non-respiratory ones, are more attributable, from a pathophysiological point of view to persistent endothelial dysfunction (28).

As reported above, L-arginine has pleiotropic effects, regulating the functions of the microcirculation through the production of NO via NO-synthase, allowing vessel dilation, reducing shear stress and acting as a regulator of the proliferation of immune system cells. In particular, increased levels of myeloid-derived immunosuppressive cells stimulated by the activity of argininase, the enzyme that opposes NO-synthase by metabolizing L-arginine into ornithine and urea, have been found in COVID19 patients with severe clinical manifestations (29, 30). Furthermore, an inverse correlation has been demonstrated between L-arginine levels and the level of platelet activation (31), responsible for hypercoagulability and contributing to the development of thromboembolic complications.

Oxidative stress is among the main vectors of inflammation (32), so the administration of vitamin C certainly proves useful in patients with Long-COVID in whom there is an underlying pro-inflammatory state, acting mainly on symptoms such as asthenia and fatigue (32, 34).

Our results were based not only on the mere attribution of a score to the severity of the symptoms reported, but also on a global and serial evaluation of the child through the COVID-related questionnaires on quality of life for specific age of the patient (Kid- & Kiddo-KINDL) which allowed us to investigate the relational sphere of the young patient, evaluating the relationship with the parent, the interaction with peers, the variation in school performance, essential elements in the developmental age. We observed a statistically significant improvement in the global score obtained at the evaluations performed at the end of the therapy with L-arginine + vitamin C compared to the changes in scores obtained in the evaluation of untreated controls.

Specifically, at T60, in comparison between groups that received the treatment *versus* Group 3, a statistically significant difference was found regarding the overall quality of life score, which in our case represented a secondary but very interesting outcome. Certainly, the improvement of symptoms in treated patients is intertwined and affects the quality of life of the young patient, improving the relationship sphere and school performance.

Our study has some limitations: the analysis was conducted on a limited sample of children with a diagnosis of Long-Covid, the randomization did not include double blinding, and parameters from respiratory function tests were not included in the follow-up assessments.

Regarding adverse reactions related to the administration of the L-arginine + vitamin C combination, none were observed, nor reported by parents, in our 24 treated patients, confirming the already existing safety data of the dietary supplement.

What occurs in the cellular microenvironment during Long-COVID (expression of pro-inflammatory cytokines, endothelial dysfunction) has many similarities with the

mechanisms underlying post-viral fatigue or Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (35), conditions that can develop in children and adults following acute infection by other viruses involved in pandemics in the recent past or endemically present (36).

The insights gained from the study on the combined treatment of L-arginine and vitamin C in pediatric Long-COVID patients prompt intriguing speculations about the potential broader applicability of this treatment regimen across various viral infections. Drawing parallels between Long-COVID and other post-viral syndromes highlights the underlying commonalities in immune dysregulation, endothelial dysfunction, and inflammation that could be targeted by this therapeutic approach (37).

By considering the pleiotropic effects of L-arginine, particularly its role in regulating microcirculation, supporting immune system functions, and protecting endothelial health, it becomes apparent that these mechanisms could have implications beyond the context of Long-COVID. In viral infections where endothelial dysfunction and inflammatory responses are prominent features, the ability of L-arginine to modulate these pathways presents a promising avenue for intervention (38). Furthermore, the antioxidative properties of vitamin C hold potential in mitigating oxidative stress-induced tissue damage and inflammation commonly observed in various viral illnesses. By reducing the burden of oxidative stress, vitamin C may contribute to a more favorable recovery trajectory and potentially lessen the severity of symptoms associated with viral infections (39).

Moreover, the emphasis on improvements in quality-of-life measures observed in the study underscores the holistic benefits that this treatment approach could offer to individuals battling other viral infections. Enhanced recovery improved social interactions, and better functional outcomes could be transformative in not just symptom management but also in restoring overall well-being in patients affected by diverse viral illnesses.

In light of these considerations, the combined treatment of L-arginine and vitamin C emerges as a multifaceted therapeutic strategy with the potential to address common pathophysiological mechanisms in viral infections beyond Long-COVID. Further exploration through clinical trials and research endeavors is warranted to elucidate the full scope of effectiveness and applicability of this treatment regimen in diverse viral contexts.

CONCLUSIONS

Long-COVID represents a possible outcome of the primary SARS-CoV2 infection, which manifests itself with multisystem symptoms and can compromise the young patient's quality of life. A combination of L-arginine and vitamin C is recommended to manage these symptoms effectively and safely. This combination has been found to be particularly useful in improving asthenia and fatigue, leading to better psychophysical and relational performance. Furthermore, treatment with L-arginine may be effective in reducing symptoms following infections caused by viral pathogens other than SARS-CoV-2, which are similar in terms of clinical manifestations, pathogenesis, and long-term outcomes.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Authors' contributions

Conceptualization: GFP, MP, SL; methodology: MP, SM; validation: SM, GP; formal analysis: SM; investigation: EL, MP; resources: GFP; data curation: EL, SM; writing-original draft preparation: EL; writing-review and editing: GFP; visualization: SM, GP; supervision: SM, SL. All Authors have read and agreed to the published version of the manuscript.

Ethical approval

Human studies and subjects

The Ethics Committee (Comitato Etico Catania 1) approved the study by deliberation 596/2021.

Data sharing and data accessibility

The Authors confirm that the data supporting the findings of this study are available within the article.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

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