Advances in Preventive Medicine and Health Care
Ratti G, et al. Adv Prev Med Health Care 4: 1043.
www.doi.org/10.29011/2688-996X.001043
www.gavinpublishers.com

Research Article

GAVIN PUBLISHERS

# Effects of bioarginina® C- Supplementation in Secondary Prevention of Post-Covid 19 High Cardiovascular Risk Patients

**Gennaro Ratti[1*], Milena Cecere[1], Federica Ratti[2], Enrico Russolillo[1], Ludovica Fulgione[3], Ofelia Martone[4], Cosimo Fulgione[4], Paolo Tammaro[1], Mario Mallardo[4]**

[1]Cardiology/ICU Department, S. Giovanni Bosco Hospital, Naples, Italy

[2]Pharmacy Department, "Federico II" University, Naples, Italy

[3]Department of Diagnostic Radiological Imaging, Maddaloni Hospital, Maddaloni (CE), Italy

[4]Cardiac Rehabilitation, S. Gennaro Hospital, Naples, Italy

[*]**Corresponding author:** *Gennaro Ratti, Cardiology/ICU Department, S. Giovanni Bosco Hospital, Naples, Italy*

**Citation:** Ratti G, Cecere M, Ratti F, Russolillo E, Fulgione L, et al. (2023) Effects of bioarginina® C- Supplementation in Secondary Prevention of Post-Covid 19 High Cardiovascular Risk Patients. Adv Prev Med Health Care 6: 1043. DOI: 10.29011/2688-996X.001043

**Received Date:** *23 November, 2023;* **Accepted Date:** *23 November, 2023;* **Published Date:** 27 November, 2023

## Background

The National Institute for Health and Care Excellence (NICE) defined post-COVID-19 syndrome as "signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis" [1,2]. Generally, initial symptoms of long COVID symptoms include fatigue (29%), muscle pain, palpitations, cognitive impairment (28%), dyspnea (21%), anxiety (27%), chest pain, and arthralgia (18%) [3,4]. This condition was below defined "Long COVID" [2]. Long COVID-19 syndrome (LCS) characterized by chronic fatigue, shortness of breath, dry cough, headache, cognitive difficulties, according to recent evidence, appears to be due to oxidative stress and endothelial dysfunction. These play critical roles in the pathophysiology of LCS. In patients at high cardiovascular risk, this condition is particularly important, especially during Cardiorespiratory Rehabilitation (CR). The complexity of the clinical feature explained by an endothelial dysfunction (pre-existing in the patient with high cardiovascular risk) is exacerbated by COVID-19 infection.

It was hypothesized that Vitamin C supplementation is effective in the prevention or cure of cardiovascular diseases. The use of liposomal Vitamin C should be preferred to other forms since liposomes might be an excellent carrier to achieve higher bioavailability [5]. Intravenous high-dose of vitamin C can reduce fatigue, cognitive impairment and pain in conditions associated with oxidative stress. It is very plausible that these effects could also be achieved in the treatment of Long COVID patients [6]. Furthermore, the functional role of L-arginine (an amino acid involved in a number of biological processes, including the biosynthesis of proteins, host immune response, urea cycle, and nitric oxide production) in the regulation of endothelial function and vascular tone, are examined in recent clinical and preclinical studies. The L-arginine supplementation was effective in hypertension, ischemic heart disease, aging, peripheral artery disease, and diabetes mellitus (7). Oral administration of L-arginine to standard therapy in patients with severe COVID-19 has significantly decreased the length of hospitalization and reduced the respiratory support at 10 days after starting the treatment (8). L-arginine has been shown to enhance response to CR regardless of age, sex and baseline function capacity and comorbid conditions [9].

## Aim of the Study

To evaluate the effects of the use of combination of oral L-arginine + liposomal vitamin C (bioarginina®C, 1.66 g 2 bottles/

day) on perceived exertion measured Borg Modified Scale (BMS) and the functional capacity measured with the six minute walking test (6MWT) of subjects with high cardiovascular risk during CR post COVID 19.

## Methods

The routine data of patients post - COVID-19 admitted to Rehabilitation of S. Gennaro Hospital (Naples) were analysed. 50 patients with high cardiovascular risk (38 M and 12 F), with mean age 58 ± 7 years, (Group A) undergoing integration with two bottles of L arginine and liposomal vitamin C were examined above for 90 days during the CR cycle. As a control population, the results obtained with standard treatment in 30 patients with high cardiovascular risk (17 M and 13 F) (mean age 61 ± 8 years) (Group B) after CR post COVID 19 infection, were examined. All patients had been positive to molecular COVID-19 nasopharyngeal swab test (for a period ranging from 15 to 30 days). The entire study lasted 3 months. In all patients at baseline and after 3 months, routine blood pressure and M and B mode echocardiogram were performed.

The ability to perform normal daily activities was analyzed with the six minute walk test (6MWT) which measures the distance that a subject can run on a flat surface, walking as fast as possible in six minutes, including any interruptions that patient deems necessary [10].

The perception of the tolerance to the effort was measured by Borg modified 0–10 Rate of Perceived Exertion (BRPE) scale [11,12]. Thirty minutes after each 6MWT, the nurse asked the patient to rate his/her level of effort at performing the exercise on the BRPE scale. The BRPE was used to measure the physical activity intensity level. BRPE is a personalized exertion grading since it gives a good estimate of heart rate during physical activity. 6 minute walk test was performed and after that patient BRPE level was graded based on Modified Borg scale grading 1-10 with 1 as "nothing", 2 as "very easy" 3 as "Easy ",4 as "comfortable",5 as "somewhat difficult",6 as "difficult",7 as "hard", 8 as "very hard",9 as "extremely hard",10 as "maximal exhaustion".

The health-related quality of life (HRQoL) was assessed by the EuroQol-5 and Dimension (EQ-5D) visual analog scale (VAS) score [13]. The EQ-5D instrument measures health status in 5 dimensions: mobility, self-care, usual activities, pain/ discomfort, and anxiety/depression. Each dimension is rated according to the following levels: a) no problems; b) some problems; c) extreme problems. The EQ-5D VAS is a quantitative measure of patients' perceived health. Patients estimated their overall health status on a 20-cm VAS with the endpoints being "best imaginable health state" (score=100) and "worst imaginable health state" (score=0). EQ5D and EQ5D-VAS were evaluated in all patients during follow up.

## Statistical Analysis

*Normally distributed variables are presented as mean ± Standard Deviation (SD) and were compared by Student's t-test for paired data for differences in the same group and with the Student's T test for unpaired data for differences between the two groups. Categorical variables are summarized in terms of number and percentages and were compared by using Chi- square test. A p-value ≤0.05 was considered statistically significant.*

## Results

The basal characteristics of patients are shown in Table 1. After 3 months, improvement in 6MWT values was observed in both groups: in Group A: 289 ± 96 m vs 419 ± 105 m ($p<0.0001$) - Group B: 280 ± 88 m vs 332 ± 98 m ($p <0.021$). However, in group A, this improvement was more significant. BRPE values are shown in Table 2. The Borg score showed a significant improvement in A group but not in group B. After the CR cycle, the increase in the 6MWT distance in group B was not accompanied by a statistically significant reduction in the Borg score, denoting a persistent muscle load. No significant differences between the 2 groups were observed in echocardiographic parameters before and after the CR cycle. No significant differences were demonstrated between the two groups in blood and echocardiographic parameters detected before and after the study period. Echocardiographic and laboratory results are shown in Tables 3 and 4. Data regarding the quality of life (without statistically significant differences at baseline) after 3 months demonstrate significant differences regarding dimensions of mobility, self-care, usual activities, pain/ discomfort but not for anxiety/depression. EQ5D and EQ5D-VAS values are shown in Table 5. Our data indicate that functional capacity, significantly reduced in high risk patients with LCS may improve after physical training. The simultaneous administration of L-arginine potentiates the response to CR, independently on age, baseline functional capacity, and comorbid conditions, so that after 3 months CR program, we were able to detect a statistically and clinically significant increase in the 6MWT distance.

| | A group 50 pts | B group 30 pts | P value |
|---|---|---|---|
| Age (yrs) | 58 ± 7 | 61 ± 8 | 0.42 |
| M/F | 38/12 | 17/13 | --- |
| BMI | 28±4 | 29±4 | 0.27 |
| Hypertension | 46 (92) | 22 (73) | 0.56 |
| Hypercholesterolemia | 39 (78) | 24 (80) | 0.75 |
| Current smoker | 9 (18) | 7 (23) | 0.98 |
| Diabetes | 28 (56) | 19 (63) | 0.21 |
| GFR<60 ml/min | 11 (22) | 7 (23) | 0.16 |
| History PCI | 41 (82) | 22 (73) | 0.35 |
| History of prior MI | 44 (88) | 28 (93) | 0.44 |

**Table 1:** *Baseline Characteristics.*

| | A group baseline | A group after 3 months | P value | B group baseline | B group after 3 months | P |
|---|---|---|---|---|---|---|
| six minute walk test (6MWT) | 289 ± 96 m | 419 ± 105 m | p <0.0001 | 280 ± 88 m | 332 ± 98 m | <0.021 |
| Borg modified 0-10 Rate of Perceived Exertion (BRPE) | 3.44 ± 3.15 | 2.46 ± 2.55 | 0.048 | 3.28 ± 2.94 | 2.71 ± 2.54 | 0.246 |

**Table 2:** *Results of 6MWT and BRPE scale.*

| | A group baseline | B group baseline | P value | A group after 3 months | B group after 3 months | P value |
|---|---|---|---|---|---|---|
| Left ventricular diastolic dimension (mm) | 51 ± 6 | 50 ± 5 | 0.46 | 49 ± 6 | 50 ± 5 | 0.88 |
| Septal thickness (mm) | 9 ± 1 | 8 ±1 | 0.27 | 9 ± 1 | 8 ±2 | 0.44 |
| Posterior wall thickness (mm) | 9 ± 1 | 8 ±1 | 0.27 | 9 ± 1 | 8 ±2 | 0.44 |
| Left atrial size | 44 ± 7 | 43 ± 6 | 0.38 | 44± 6 | 43 ± 5 | 0.42 |
| Left ventricular ejection fraction (%) | 52 ± 7 | 51 ± 7 | 0.17 | 53 ± 4 | 51 ± 2 | 0.02 |
| Right ventricular basal diameter (mm) | 27 ± 2 | 28 ± 5 | 0.98 | 26 ± 3 | 27 ± 3 | 0.49 |
| Tricuspid annular plane systolic excursion, TAPSE (mm) | 25 ± 1 | 27 ± 3 | 0.062 | 24± 2 | 24± 1 | 0.91 |
| Pulmonary artery systolic pressure (mmHg) | 33 ± 8 | 31 ± 7 | 0.44 | 32 ± 9 | 32 ± 7 | 0.92 |

**Table 3:** *Echocardiographic findings.*

| | A group baseline | B group baseline | P value | A group after 3 months | B group after 3 months | P value |
|---|---|---|---|---|---|---|
| Glucose (mg/dL) | 86 ± 15 | 88 ± 16 | 0.50 | 90 ± 14 | 95 ± 15 | 0.12 |
| Creatinine (mg/dL) | 0.7 ± 0.24 | 0.7 ± 0.23 | 0.42 | 0.8 ± 0.2 | 0.7 ±2 | 0.44 |
| BUN (mg/dL) | 53 ± 15 | 50 ±16 | 0.33 | 51 ± 17 | 52 ±14 | 0.75 |
| Sodium (mEq/L) | 140 ± 4 | 141 ± 4 | 0.45 | 140 ± 5 | 140 ± 4 | 0.42 |
| Potassium (mEq/L) | 4.7 ± 0.5 | 4.6 ± 0.5 | 0.64 | 4.7 ± 0.4 | 4.6 ± 0.6 | 0.19 |
| Hemoglobin (g/dL) | 14.3 ± 1.3 | 14.1 ± 1.3 | 0.55 | 14.3 ± 1.5 | 14.2 ± 1.5 | 0.97 |
| AST (U/L) | 33 ± 14 | 34 ± 20 | 0.76 | 33 ± 14 | 32 ± 17 | 0.53 |
| ALT (U/L) | 34 ± 14 | 33 ± 15 | 0.89 | 33 ± 13 | 34 ± 11 | 0.47 |

**Table 4:** *Laboratory Results.*

| | A group Baseline 50 pts n(%) | B group Baseline 30 pts n(%) | P-value | A group after 3 months 50 pts n(%) | B group after 3 months 30 pts n(%) | P-value |
|---|---|---|---|---|---|---|
| **EQ-5D** | | | | | | |
| **Pain/discomfort, no. (%)** | | | | | | |
| I have no pain/discomfort | 39 (78) | 28(92) | 0.72 | 48 (96) | 24(80) | 0.02 |
| I have moderate pain/discomfort | 9 (18) | 1 (4) | 0.054 | 2 (4) | 5 (16) | 0.6 |
| I am in extreme pain/discomfort | 2 (4) | 1(4) | 0.02 | 0 | 1(4) | 0.19 |
| **Anxiety/depression, no. (%)** | | | | | | |
| I am not anxious or depressed | 36 (72) | 25(84) | 0.24 | 45 (90) | 27(90) | 1.0 |
| I am moderately anxious or depressed | 11 (22) | 4 (14) | 0.33 | 5 (10) | 3(10) | 1.0 |
| I am extremely anxious or depressed | 3 (6) | 1(2) | 0.28 | 0 | 0 | ns |
| **Mobility, no. (%)** | | | | | | |
| I have no problems in walking about | 40 (80) | 22 (74) | 0.48 | 46 (92) | 24 (80) | 0.11 |
| I have some problems in walking about | 8 (16) | 6 (20) | 0.64 | 4(8) | 6 (20) | 0.11 |
| I am confined to bed | 2 (4) | 2(6) | 0.59 | 0 | 0 | ns |
| **Self-Care, no. (%)** | | | | | | |
| I have no problems with self-care | 47 (94) | 22(74) | 0.009 | 49 (98) | 23 (76) | 0.002 |
| I have some problems washing or dressing myself | 2 (4) | 5 (17.9) | 0.052 | 1 (2) | 4 (13) | 0.042 |
| I am unable to wash or dress myself | 1 (2) | 3 (10) | 0.11 | 0 | 3 (11) | 0.022 |
| **Usual Activities (e.g. work, study, housework, family or leisure activities), no. (%)** | | | | | | |
| I have no problems with performing my usual activities | 44 (88) | 23(77) | 0.18 | 48 (96) | 23 (77) | 0.008 |

| | | | | | | |
|---|---|---|---|---|---|---|
| I have some problems with performing my usual activities | 4 (8) | 5 (17) | 0.65 | 2 (4) | 6 (21) | 0.02 |
| I am unable to perform my usual activities | 2 (4) | 2 (6) | 0.59 | 0 | 1 (2) | 0.19 |
| **EQ5D-VAS values** | 62±11 | 66±15 | 0.16 | 77±14 | 70±16 | 0.032 |

**Table 5:** Health-related quality of life.

## Conclusion

We hypothesized that a supplementation combining L-Arginine (to improve endothelial function) and Vitamin C (to reduce oxidation) could have favorable effects on Long- COVID symptoms. In the CR program, the introduction of nutritional supports, vitamins and amino acids, can be considered a useful approach to LCS. Our data confirm the improvement in the physical performance of post COVID 19 patients with introduction of nutritional supports with L- arginine and liposomal vitamin C, in terms of reducing its typical symptoms and improving the perceived tolerance to effort.

Our results do not allow any speculation on the mechanisms underlying the favorable effect of L- arginine on CR-induced improvement in physical capacity. However, LCS leads to endothelial dysfunction with inflammation and oxidative stress, contributing to physical impairment, hospitalizations, and mortality.

## References

1. National Institute for Health and Care Excellence (2020) COVID-19 rapid guideline: managing the long-term effects of COVID-19. Manchester: London.
2. Gyöngyösi M, Alcaide P, Asselbergs FW, Brundel BJJM, Camici GG, et al. (2023) Long COVID and the cardiovascular system-elucidating causes and cellular mechanisms in order to develop targeted diagnostic and therapeutic strategies: a joint Scientific Statement of the ESC Working Groups on Cellular Biology of the Heart and Myocardial and Pericardial Diseases. Cardiovasc Res 119: 336-356.
3. Carfi A, Bernabei R, Landi F (2020) Persistent Symptoms in Patients After Acute COVID-19. JAMA 324: 603-605.
4. Koc HC, Xiao J, Liu W, Li Y, Chen G (2022) COVID and its Management Int J Biol Sci 18: 4768-4780.
5. Morelli MB, Gambardella J, Castellanos V, Trimarco V, Santulli G (2020) Vitamin C and Cardiovascular Disease: An Update. Antioxidants 9: 1227.
6. Vollbracht C, Kraft K (2022) Oxidative Stress and Hyper-Inflammation as Major Drivers of Severe COVID-19 and Long COVID: Implications for the Benefit of High-Dose Intravenous Vitamin C. Front Pharmacol 13: 899198.
7. Gambardella J, Khondkar W, Morelli MB, Wang X, Santulli G, et al. (2020) Arginine and Endothelial Function. Biomedicines 8: 277.
8. Fiorentino G, Coppola A, Izzo R, Annunziata A, Bernardo M, et al. (2021) Effects of adding L-arginine orally to standard therapy in patients with COVID-19: A randomized, double-blind, placebo-controlled, parallel-group trial. Results of the first interim analysis. EClinicalMedicine 40: 101125.
9. Mone P, Izzo R, Marazzi G, Manzi MV, Gallo P, et al. (2022) L-Arginine Enhances the Effects of Cardiac Rehabilitation on Physical Performance: New Insights for Managing Cardiovascular Patients During the COVID-19 Pandemic. J Pharmacol Exp Ther 381: 197-203.
10. Enright PL, Sherrill DL (1998) Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 158: 1384-1387.
11. Borg G (1998) Borg's Perceived Exertion and Pain Scales. Champaign, IL: Human Kinetics. p. 104.
12. Borg DN, Costello JT, Bach AJ, Stewart IB (2017) Perceived exertion is as effective as the perceptual strain index in predicting physiological strain when wearing personal protective clothing. Physiol Behav 169: 216-223.
13. Rabin R, de Charro F (2001) EQ-5D: a measure of health status from the EuroQol Group. Ann Med 33: 337-343.