Six-Week Oral Guanidinoacetic Acid Administration Improves Muscular Performance in Healthy Volunteers

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Background: Guanidinoacetic acid (GAA), a natural precursor of creatine, is a new promising dietary supplement, yet its performance-enhancing effect, if any, has yet to be established. The purpose of this pilot study was to evaluate the effects of supplemental GAA on muscle strength, anaerobic performance, and aerobic performance in healthy men and women.

Method: The study enrolled 48 young participants (age, 22.3 ± 1.5 years; height, 176.4 ± 10.0 cm; weight, 71.9 ± 14.3 kg), who received oral doses of GAA (1.2, 2.4, or 4.8 g/d) for 6 weeks in a randomized, double-blind, placebo-controlled trials.

Results: Significant differences were observed between treatment groups for handgrip strength among participants receiving 1.2 g of GAA per day and 2.4 g of GAA per day, as compared with placebo ($P < 0.05$). In addition, muscle endurance expressed as the change from baseline in repetitions performed in the bench press exercise was significantly greater in the 1.2 g/d dose of GAA ($P = 0.01$) and the 4.8 g/d dose ($P = 0.01$) compared with placebo. No dose-response differences were found between trials.

Conclusions: Results from this preliminary study indicate that supplemental GAA ingested in young individuals can improve exercise performance, even at low doses (1.2 g/d).

Key Words: creatine, guanidinoacetic acid, muscle strength, endurance

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Guanidinoacetic acid (GAA) is a natural precursor of creatine (Cr). It is essential for energy metabolism in energy-demanding tissues (eg, muscle, nerve), with GAA mainly produced by the kidney and pancreas.[1] Guanidinoacetic acid was identified as an endogenous substance in humans about 80 years ago[2] and has draws attention in recent years as a promising new dietary agent because of its Cr-recovery effect, high bioavailability, and cost-effectiveness.[3] Guanidinoacetic acid deficiency can occur because of impairment in endogenous synthesis and/or increased requirements during energy-demanding circumstances.[4,5] Low GAA availability may impede cellular bioenergetics, which suggests a need for GAA replenishment from exogenous sources. Because the uptake of GAA through the diet is negligible (eg, meat GAA content is generally below 10 mg/kg),[6] provision of concentrated GAA in oral form may supplement the diet, making GAA eligible as a functional food ingredient or dietary additive. Several recent studies confirmed the GAA- and Cr-loading effect of supplemental GAA,[7–9] yet its use in human nutrition is hindered by limited knowledge on the physiological effectiveness of GAA supplementation. In addition, there is little information available about the effects of exogenous GAA on exercise performance. Since GAA stimulates Cr synthesis, exogenously provided GAA may increase Cr concentrations and enhance muscular force and power. This might be particularly important for patients with muscle weakness, chronic fatigue syndrome, and mitochondrial diseases, or athletes. Previously, animal studies have demonstrated performance-enhancing effects of GAA when administered as feed additive.[10–12] As such, we hypothesize that supplemental GAA may enhance exercise performance in humans, while the magnitude of effect may be dose dependent. Thus, the purpose of this preliminary study was to compare the effects of 6 weeks of 3 different GAA supplementation protocols (1.2, 2.4, and 4.8 g/d) on muscle strength, anaerobic performance, and aerobic performance in healthy men and women. Exploring the changes in exercise performance consequent to exogenous GAA loading seems to be an important step in examining the effectiveness of GAA when consumed on a daily basis.

MATERIALS AND METHODS

The original randomized, double-blind, placebo-controlled study was initiated in 2009 to examine the safety and metabolic effects of medium-term supplementation of oral GAA in healthy men and women. Detailed study design and protocol have been published previously.[13] In brief, the study enrolled 48 young healthy participants (24 men and 24 women; age, 22.3 ± 1.5 years; height, 176.4 ± 10.0 cm; weight, 71.9 ± 14.3 kg), who received either an oral dose of GAA (1.2, 2.4, and 4.8 g/d) or a placebo for 6 weeks. Approval of the institutional review board was obtained with all procedures performed in accordance with the Declaration of Helsinki. During the study, additional analyses of the original data set were introduced to explore their association with GAA administration.[7–9] For this report, exercise performance outcomes were observed at baseline and after 6 weeks of intervention. Isometric strength of forearm muscles was assessed by handgrip dynamometer (Jamar J00105; Lafayette Instrument Company, Lafayette, IN). Muscular endurance in the upper and lower body was assessed through maximal number of full repetitions in the supine free-weight bench press (75% of body mass) and leg press (45 degrees, 150% of body mass) exercises, respectively. Single and repetitive maximal vertical jump performance was assessed using a contact mat (Just Jump System; Probotics, Huntsville, AL). Jump height as well as both peak anaerobic power and mean anaerobic power were recorded. Aerobic performance was assessed by a maximal endurance running test, with gas exchange data collected throughout the test using a breath-by-breath metabolic system (Vacu-Med CPX; Ventura, CA). All participants were familiarized with testing procedures and were assessed on the same day with the tests performed in the same order. The primary end point with respect to the efficacy in exercise performance was the increase in muscle endurance on the bench press test, achieving a significant (5%) change in number

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of repetitions from baseline to 6 weeks. The primary analyses of estimated between-group differences were performed on data from the modified intention-to-treat population. Initially, data were tested with Shapiro-Wilk test for the normality of distribution, and with Bartlett test for the homogeneity of the variances. Baseline characteristics were compared with 1-way analysis of variance (ANOVA). When homogenous variances were verified for normally distributed data, 2-way mixed model ANOVA with repeated measures was used to establish if any significant differences existed between participants' responses over time of intervention (0 vs 6 weeks). In the event of a significant F ratio, post hoc analyses were performed with a Tukey honest significant difference test to identify the differences between individual sample pairs. When nonhomogenous variances were identified, data analyses were performed using the 4 independent samples Kruskal-Wallis test, with a Games-Howell post hoc test used to evaluate between-group differences. Significance level was set at $P \leq 0.05$. The data were analyzed using the statistical package SPSS version 21.0 (SPSS Inc, Chicago, IL).

RESULTS

Forty-eight participants underwent randomization and received at least 1 dose of a study supplement; 12 participants per group were randomly assigned to each GAA group and placebo group. Baseline characteristics of the intention-to-treat population were generally similar in the GAA and placebo groups (Table 1). A total of 91.6% of the participants in the placebo group and 91.6%, 100%, and 91.6% in the 1.2, 2.4, and 4.8 g/d GAA groups, respectively, completed the study. No participant withdrew from the study because of any adverse event. Compliance was 86.3% for GAA groups and 95.1% for the placebo group.

Changes in exercise performance end points from baseline to week 6 are presented in Table 2. Significant differences in handgrip strength were seen between the groups. After 6 weeks of GAA ingestion, participants receiving 1.2 g of GAA per day and 2.4 g of GAA per day significantly improved their handgrip strength compared with placebo ($P < 0.05$). Furthermore, muscle endurance expressed as the change from baseline in repetitions performed in the bench press exercise was significantly greater in the 1.2 g/d dose of GAA ($P = 0.01$), and the 4.8 g/d dose ($P = 0.01$) compared with placebo. No significant between-group changes were observed at week 6 in lower body muscle endurance, nor anaerobic or aerobic performance. In addition, changes in body mass index (weight in kilograms divided by height in meters squared) during the 6-week intervention seemed to be similar in all treatment groups ($P = 0.41$).

DISCUSSION

The results of this study indicated that 6 weeks of GAA supplementation, without a concomitant exercise program, can increase grip strength and upper body muscle endurance in healthy men and women. Daily ingestion of up to 4.8 g of GAA for 6 weeks improved upper body muscular fitness (up to ~25%), whereas other aspects of exercise performance were not affected by the intervention. Dose-response relationships between GAA administration and exercise performance outcomes were not found for the dose range investigated. Supplemental GAA seems to improve both isometric and dynamic exercise performance.

Use of supplemental GAA in human nutrition and medicine dates back to the 1950s, when beneficial effects of GAA (also known as glycocyamine) was reported in patients experiencing from congestive heart failure, cardiac decompensation, rheumatic disease, and neuromuscular disorders.[14–16] Treatment with GAA was usually provided in dosages of up to 5 g/d, which led to a reduction in fatigue, improved strength and endurance, and an improved sense of well-being.[14] Authors suggested that the positive effects of GAA were mediated by an enhanced synthesis of Cr, providing additional energy for cellular bioenergetics. Preliminary human studies have provided limited objective data on exercise performance, and no study used a randomized, double-blind, placebo-controlled design. In this present study, GAA ingestion of up to 2.4 g/d increased handgrip strength approximately 6 kg as compared with the placebo, suggesting performance-enhancing effect of GAA on maximal isometric strength of the hand and forearm muscles. In addition, GAA significantly improved muscular endurance in the upper body as assessed through bench press performance, with number of repetitions increased for up to 8.9 with the high-dose GAA, as compared with the placebo. We also

TABLE 1. Baseline Characteristics of the Study Population by Treatment Group*

Characteristic	Placebo (n = 12)	GAA 1.2 g/d (n = 12)	GAA 2.4 g/d (n = 12)	GAA 4.8 g/d (n = 12)	*P*
Age, y	22.1 (1.2)	22.3 (1.4)	22.1 (1.8)	22.5 (1.7)	0.89
Training experience, y	3.4 (1.1)	3.9 (1.1)	3.1 (0.8)	3.3 (1.1)	0.25
Body mass index, kg/m^2	22.5 (2.1)	23.3 (3.3)	22.1 (1.6)	23.3 (1.9)	0.47
Handgrip strength, kg	84.3 (27.9)	92.3 (28.2)	87.3 (23.5)	92.8 (26.4)	0.84
Bench press, no. repetitions	18.0 (10.1)	20.1 (14.1)	22.8 (21.3)	22.5 (18.0)	0.88
Leg press, no. repetitions	28.2 (15.5)	32.4 (11.6)	25.5 (14.6)	27.2 (16.4)	0.69
Vertical jump, cm	37.6 (10.3)	38.2 (9.8)	39.2 (9.6)	37.8 (10.9)	0.98
Peak anaerobic power, W/kg	13.2 (1.8)	13.3 (1.7)	13.5 (1.7)	13.2 (1.9)	0.98
Mean anaerobic power, W/kg	11.0 (1.6)	10.0 (1.4)	10.6 (1.4)	10.4 (1.5)	0.78
$V_{O_{2max}}$, mL/kg per min†	45.8 (3.4)	47.0 (4.5)	47.4 (3.7)	47.4 (5.4)	0.79
Ventilatory threshold, % $V_{O_{2max}}$	78.2 (8.9)	79.1 (4.8)	82.0 (7.5)	80.6 (7.2)	0.59
Peak velocity, km/h	14.7 (1.7)	14.1 (1.6)	14.2 (1.9)	14.1 (1.9)	0.83
Time to exhaustion, s	495 (110)	484 (90)	481 (95)	436 (132)	0.56

*Values are presented as mean (SD).

†Comparisons between the GAA groups and placebo group were performed with the use of a 4-sample 1-way ANOVA for continuous variables and Kruskal-Wallis test for categorical variables. There were no significant between-group differences in any of the listed characteristics.

$V_{O_{2max}}$ indicates maximal oxygen uptake.

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TABLE 2. Changes in Exercise Performance End Points From Baseline to Week 6*

	Placebo	GAA 1.2 g/d			GAA 2.4 g/d			GAA 4.8 g/d		
End Point	**Change**	**Change**	**Least Squares Mean Difference From Placebo (95% CI)**	***P***	**Change**	**Least Squares Mean Difference From Placebo (95% CI)**	***P***	**Change**	**Least Squares Mean Difference From Placebo (95% CI)**	***P***
Handgrip strength, kg	−3.5 ± 2.3	2.0 ± 1.1	5.5 (0.3−10.7)	0.03	3.0 ± 1.8	6.5 (0.5−12.5)	0.04	−3.8 ± 2.5	−0.3 (−7.3 to 6.7)	0.91
Bench press, no. repetitions	0.4 ± 0.9	5.0 ± 1.1	4.6 (1.6−7.6)	0.01	3.6 ± 1.2	3.2 (0.0−6.4)	0.09	5.8 ± 1.4	5.4 (1.9-8.9)	0.01
Leg press, no. repetitions	2.0 ± 1.9	14.7 ± 7.5	12.7 (−3.4 to 28.8)	0.15	15.8 ± 5.6	13.8 (1.1−26.5)	0.07	7.7 ± 4.1	5.7 (−3.7 to 15.1)	0.27
Vertical jump, cm	1.3 ± 1.2	0.9 ± 0.8	−0.4 (−3.5 to 2.7)	0.81	0.6 ± 0.9	−0.7 (−3.8 to 2.4)	0.56	−0.4 ± 1.4	−1.7 (−5.6 to 2.18)	0.26
Peak anaerobic power, W/kg	0.25 ± 0.21	0.14 ± 0.17	−0.11 (−0.67 to 0.45)	0.74	0.09 ± 0.16	−0.16 (−0.72 to 0.40)	0.51	0.01 ± 0.25	−0.24 (−0.93 to 0.45)	0.36
Mean anaerobic power, W/kg	−0.64 ± 0.32	−0.59 ± 0.30	−0.05 (−0.96 to 0.86)	0.92	−0.45 ± 0.24	−0.19 (−1.01 to 0.63)	0.71	−0.33 ± 0.19	−0.31 (−1.08 to 0.46)	0.42
Time to exhaustion, s	−16.4 ± 13.4	28.2 ± 13.4	44.6 (5.1−84.1)	0.07	16.3 ± 15.6	32.7 (−10.5 to 75.9)	0.11	−3.2 ± 13.7	−13.2 (−26.7 to 53.1)	0.48
Ventilatory threshold, % Vo_{2max}	1.5 ± 1.9	3.8 ± 2.0	2.3 (−3.5 to 8.1)	0.44	−0.8 ± 2.3	−2.3 (−8.6 to 4.0)	0.39	1.6 ± 1.8	0.1 (−5.3 to 5.5)	0.98
Vo_{2max}, mL/kg per min	2.9 ± 1.8	4.1 ± 1.1	1.2 (−3.2 to 5.6)	0.57	3.2 ± 0.9	0.3 (−3.7 to 4.3)	0.83	2.9 ± 2.0	0 (−5.5 to 5.5)	0.87
Peak velocity, km/h	0.6 ± 0.3	1.5 ± 0.6	0.9 (−0.6 to 2.4)	0.25	1.5 ± 0.4	0.9 (−0.1 to 1.9)	0.22	0.5 ± 0.3	−0.1 (−1.0 to 0.8)	0.58

*Values are presented as least squares mean ± SE, unless otherwise specified. The analyses were performed in the modified intention-to-treat population. *P* values are unadjusted.

Vo_{2max} indicates maximal oxygen uptake.

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reported a trend for improved lower body muscle endurance after 6 weeks of GAA supplementation. Guanidinoacetic acid ingestion seemed to have no ergogenic effect on aerobic or anaerobic performance. Our research confirmed the results of recent animal studies that demonstrated muscle performance-enhancing characteristics of supplemental GAA.[6] Addition of GAA as a feed additive to broilers diet improved energy management and animal performance as reflected by an increase in skeletal muscle growth and contractile activity of breast muscles.[11] It seems that exogenous GAA ingestion can provide an ergogenic benefit with emphasis on specific muscle groups. Because the upper body is less developed in the general population as compared with the lower body,[17] GAA supplementation might be particularly effective for enhancing force production in specific muscle groups with lower initial levels of strength at presupplementation (eg, chest, shoulders, arms). Therefore, GAA may have a greater effect on the relative strength gains in individuals with lower level of muscular fitness or novice athletes. These findings warrant future considerations. In addition, further studies are needed to evaluate performance-enhancing effects of oral GAA in diseases and conditions with poor exercise capacity and/or exercise intolerance (eg, chronic fatigue syndrome, mitochondrial diseases, cardiorespiratory disorders, heart conditions).

Several mechanisms could be proposed to explain the ergogenic effects seen after supplementation of GAA. Because GAA acts as a direct precursor of Cr, exogenous GAA may stimulate the production of Cr in the liver, elevate intramuscular stores of Cr, and improve Cr-dependent muscular performance. We recently confirmed the Cr-recovery effect of exogenous GAA, with a significant increase in fasting serum Cr (up to 50%) after 6 weeks of supplementation with 2.4 g/d of GAA.[7] However, no human studies so far investigated the effects of exogenous GAA on intramuscular levels of Cr over time. If Cr content in skeletal muscle is increased by GAA administration, it may elicit improvements in exercise performance through different means.[18] Another hypothesis suggests that exogenous GAA might positively affect metabolic utilization of arginine,[3] which may increase muscular growth and performance. Guanidinoacetic acid spares dietary arginine and yields a marked performance response when added to a 20% protein arginine-deficient casein diet in young chicks.[10] Further studies are needed to investigate if arginine-related effect of exogenous GAA has practical significance for muscular gain in human physiology. Finally, the interaction of GAA with γ-aminobutyric acid (GABA) A receptors[19] might represent another candidate mechanism explaining performance-enhancing effects of this compound. Guanidinoacetic acid might partially downregulates GABA synthesis in GABA-ergic peripheral neurons and skeletal muscle,[20] which could affect muscular tone and exercise performance. In addition, because of the fact that GAA is categorized as a nutritional additive from the group of amino acids, salts, and analogs, its use is allowed in sport during competition at the present time, and not prohibited by the World Anti-Doping Agency.[21] Therefore, the administration of GAA might be considered as an innovative and legitimate way to improve exercise performance, as opposing to anabolic steroids or growth hormone that allow for abuse during sport competition. It seems that performance translate to true benefit of exercising after GAA intervention, with GAA viewed as relatively safe food additive. However, before accepting GAA as a novel performance-enhancing dietary supplement in human nutrition, several regulation issues should be addressed as well. From a regulatory perspective, GAA has never been cataloged or authorized either in the United States or in Europe as a dietary ingredient or novel food. The safety of GAA for human consumption is not yet approved by competent authorities like the U.S. Food and Drug Administration or the European Food Safety Authority. Currently, GAA should be perceived as an experimental nutritional substance rather than an officially accredited dietary supplement.

Guanidinoacetic acid had an acceptable adverse effects profile when orally administered in healthy men and women, with liver and muscle enzyme profiles not affected by GAA intervention and rather low incidence of adverse events after ingestion.[7] In addition, European Food Safety Authority concluded that GAA did not have mutagenic or genotoxic properties.[6] However, because dietary GAA drives increased homocysteine production,[9] prolonged administration might affect total serum homocysteine, a potential risk factor for cardiovascular diseases. Therefore, a possible administration of GAA in cardiovascular patients needs careful monitoring of serum homocysteine and dose titration trial during administration. Furthermore, no studies so far have evaluated the potential vasoactivity of GAA and blood pressure responses to GAA intervention. Although accepted as a safe additive at the moment, more studies are needed to evaluate long-term safety of GAA in clinical environment.

In conclusion, supplemental GAA improved muscular performance when administered for 6 weeks in healthy men and women, with no dose-response differences found between trials. As a more stable and less expensive alternative to Cr,[3] GAA can be used as ergogenic agent even at low doses (1.2 g/d) to enhance upper body strength. Exact mechanism of ergogenic action of GAA is yet to be revealed.

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