2020, Volume 3 (Issue 3): 9 OPEN ACCESS

# Inositol-Stabilized Arginine Silicate Improves Post-Exercise Cognitive Function in Recreationally Active, Healthy Males: A Randomized, Double-Blind, Placebo-Controlled Crossover Study

*Original Research*

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**Abstract**

**Introduction:** At all competition levels, athletic performance depends on simultaneously handling physiological and cognitive demands. The objective of this study was to determine the efficacy of a patented complex of inositol-stabilized arginine silicate (ASI; Nitrosigine®) to improve cognitive performance following intense exercise.

**Methods:** Twenty-four healthy, recreationally active males (26.50 ± 4.85 years, 25.31 ± 2.52 kg/m² BMI) were enrolled in this randomized, double-blind, placebo-controlled crossover study. A single oral dose of 1500 mg ASI or placebo was administered 30 minutes before a maximally graded exercise test. Prior to and following exercise, cognitive function was assessed via the Trail Making Test (TMT). Safety was evaluated at end of study.

**Results:** Following intense exercise, ASI reduced the time to complete TMT Part A and B (2.80 ± 5.97, 5.54 ± 3.77 seconds, respectively) compared to increased time with placebo (19.82 ± 4.58, 7.68 ± 5.06 seconds, respectively). Differences between ASI and placebo were statistically significant ($p = 0.01$ TMT A, $p = 0.05$ TMT B). ASI was found to be safe and well-tolerated with no related adverse events.

**Conclusion:** Intense exercise resulted in impaired cognitive function, which was prevented by pre-exercise ASI consumption. Future research should examine the efficacy of ASI in athletes, as improvement in cognitive function would be advantageous through enhanced ability to process complex information in quickly changing games or events.

***Key Words:*** Cognitive flexibility, sports performance, nitric oxide

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*Published July 6, 2020*

## Introduction

Sports performance, at all levels of competition, is highly dependent on ability to simultaneously manage physiological and cognitive demands[1]. Cognitive flexibility, specifically with respect to decision making, communication and perception, may enhance exercise performance by modulating anxiety and stress[2]. This is supported by the fact that elite athletes demonstrate superior cognitive abilities compared to inexperienced athletes[3,4]. Moreover, mental fatigue caused by cognitively demanding tasks has been shown to limit exercise tolerance and increase perceived exhaustion[5]. Research examining effects of exercise on cognition is less consistent. While some individuals feel enhanced cognitive performance following exercise, intense exercise can also cause mental disorientation and disrupt decision making. The varied effects on cognition can be attributed to the type and intensity of exercise and individual physical activity level. A recent meta-analysis found that acute treadmill running led to impaired cognitive performance, while cycling was associated with improvements[6]. The cognitive task selected also strongly influenced performance[6]. Reallocation of energetic resources during acute strenuous exercise may contribute to feelings of mental fatigue and subsequent

cognitive impairments[7]. Given the two-way relationship between exercise and cognitive function, it is important that elite and recreational athletes, as well as active individuals, are in their most prominent physical and mental states.

Sports nutrition supplements boast marketing claims such as overall health status improvement, physical or cognitive performance enhancement, increase in energy, and attenuation of pain. Common ingredients used by both trained and untrained individuals include protein, creatine, caffeine, and amino acids[8,9]. Arginine, a nonessential amino acid, is the substrate for nitric oxide (NO) synthase, which converts it to citrulline, and synthesizes NO in the process[8,10-15]. Arginine has demonstrated its potential to improve aerobic and resistance exercise performance and recovery due to its ability to increase NO production and subsequent vasodilation. However, these findings are not consistent across all studies[8,10-15], warranting further investigation. Vasodilation results in increased oxygen and nutrient delivery to active muscles and waste product removal during exercise[10]. While the endogenous physiological actions of NO in the central nervous system (CNS) have been reviewed extensively[16], its potential to enhance cognitive performance during exercise is not firmly established. Numerous publications show the critical roles of NO on the CNS in neurotransmitter release, neuroplasticity, and mental well-being[16,17]. In animals, both arginine and NO have also shown positive effects on learning, memory, and synaptic plasticity, as well as neuroprotective effects in the brain[16,18,19]. The significant role of NO and arginine on the CNS is supported by clinical research demonstrating that arginine can reduce mental stress and anxiety in healthy subjects[17]. Arginine's role in CNS health and function is of special interest.

The discovery of increased bioavailability of arginine when bound to silicon[20,21] led to the development of a novel sports nutrition ingredient, Nitrosigine® (inositol-stabilized arginine silicate; ASI)[14,21]. ASI is stable in powder form and soluble in aqueous solutions[22]. The safety of a 14-day supplementation with 1500 mg ASI has been demonstrated, along with increased serum levels of arginine, silicon, and NO in ten healthy males[21]. A 4-day supplementation with 1500 mg ASI increased perceived energy levels and decreased fatigue in 16 healthy males[23]. The same dose of ASI for 14 days also improved cognitive performance after 10 minutes, 3 days, and 14 days of supplementation compared to placebo[14]. The effect of ASI on post-exercise cognitive function in healthy, recreationally active individuals has yet to be investigated. The current study explored the efficacy of an acute oral dose of ASI on cognitive performance and safety following an intense bout of exercise in a healthy, recreationally active male population.

## Methods

*Study Design and Ethics Approval*

This randomized, double-blind, placebo-controlled, exploratory crossover study was conducted at KGK Science Inc., London, ON Canada. The study consisted of two single-day study periods separated by a two-week washout (Figure 1). An independent Institutional Review Board (Aurora, Ontario, Canada) granted unconditional approval. The study was performed according to the Declaration of Helsinki guidelines and approved by the Natural and Non-Prescription Health Product Directorate, Health Canada.

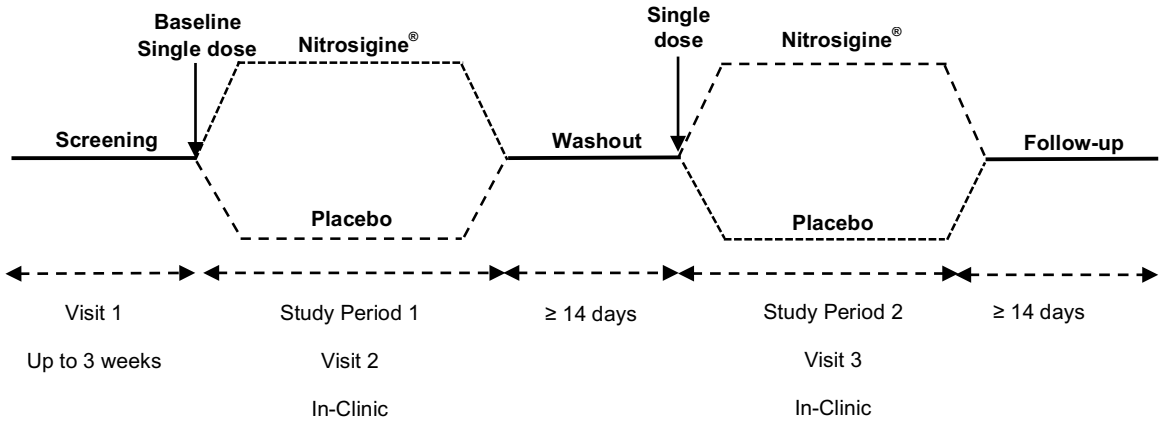


Figure 1. Schematic representation of clinical trial design. Twenty-four participants were enrolled in this double-blind, randomized, placebo-controlled, crossover study. All but two participants enrolled in the study completed all study-related assessments at all study visits.

*Participants*

Healthy male adults with a self-reported exercise history of less than 90 minutes per week for the last 6 months were recruited from Southwestern Ontario, Canada. Volunteers were deemed healthy as per physical exam, laboratory results, medical history, and electrocardiogram (ECG).

Exclusion criteria included: Use of nutritional supplements containing arginine and/or silicon within the previous 14 days and/or creatine within 30 days; use of calcium beta-hydroxy-beta-methylbutyrate, L-carnitine, Eleuthero, Panax ginseng, lysine supplements, silicates containing antacids, or St. John's wort within 30 days; health disease or conditions including but not limited to cardiovascular, respiratory, or musculoskeletal conditions, thyroid disease, diabetes, cancer, bleeding or psychiatric disorders; or any other condition which may have adversely affected the volunteer's ability to complete the study or which posed significant risk to them.

*Randomization and Blinding*

An unblinded individual at the study site not involved in study assessments prepared a randomization schedule, and enrolled participants were assigned a unique 6-digit number based on a randomization list (www.randomization.com). Treatment allocation was implemented based on these numbers. Sealed, labeled opaque envelopes contained the associated treatment for a participant.

*Outcome Measures*

The effect of ASI on cognitive function was evaluated using the Trail Making Test (TMT), a well-established measure of processing speed and executive functioning[24,25]. Time to complete each of the two parts, A and B, was measured. TMT Part A involves connecting a sequence of 25 numbers in ascending order. Part B is similar with respect to connecting elements in an ascending order, but for an alternating sequence of 25 numbers and letters. Safety outcomes included pre- and post-emergent adverse events, vitals (blood pressure and heart rate), blood chemistry and hematology. Blood samples were obtained by venipuncture. Hematology (complete blood count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell count, hemoglobin, hematocrit, platelets, RBC indices) and clinical chemistry (alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, electrolytes, estimated glomerular filtration rate) were measured by a central laboratory (LifeLabs, London, ON).

*Protocol*

At the screening visit (visit 1), subjects were deemed healthy, eligibility was assessed, and a Maximally Graded Exercise test (mGXT) was completed to volitional fatigue. Participants were required to run until volitional exhaustion, or the test was complete. A complete test was defined as reaching a $VO_2$ plateau followed by two, consecutive, lower readings. The test was also ended if the participant had concomitant contraindicated physiological changes. The test started with a 5-minute warmup where the speed was set to 2.5 mph and increased by the participant until they reached a self-selected pace they felt could be maintained for 20 minutes. After the warmup, each stage of the test protocol was 2 minutes long. For the first 4 stages, the grade of the treadmill was increased by 1.5%, 4.5%, 7.5%, and 10%, respectively. After stage 4 was complete, the treadmill speed was increased by 0.5 mph until the test termination criteria were met. The self-selected pace of each participant during the screening visit was recorded and used for subsequent testing. Eligible participants arrived for visit 2 fasted for 12 hours, had a physical exam and were randomized into either the ASI→placebo or placebo→ASI sequence. Immediately after consuming a standardized breakfast (one bagel with cream cheese, or jam for participants with lactose-intolerant allergies, and apple juice), participants completed TMT Part A and B. Fifteen minutes after breakfast, participants consumed the study product, dissolved into 296 mL of room temperature tap water, and 30 minutes post-study product consumption, the mGXT was completed. Participants completed the mGXT, described above, at the pace selected in the screening visit. Subjects continued until no longer able to run or coordinators deemed the test complete as above.

After the 2-week washout, participants returned to the clinic and crossed over to be administered the product they did not receive during the first study period. All assessments from the first study period were repeated. Adverse events were recorded between all periods and for 2 weeks after the second.

*Investigational Product*

The investigational product, ASI (1500 mg) as Nitrosigine®, and placebo were provided by Nutrition 21, LLC, Purchase, NY, USA as identical stick packs. No differences in size, colour, taste, texture, or packaging were detectable. ASI packs contained arginine, silicon, inositol, and potassium with excipients citric acid, natural flavour, sucralose, acesulfame potassium, and Red 40. The placebo contained maltodextrin and the same excipients as ASI. Products were labeled according to the requirements of the ICH-GCP guidelines and applicable local regulatory guidelines. They were coded by a KGK staff member not involved in conducting the study and included the applicable randomization number. Products were stored in a lockable room with controlled temperature and humidity and no exposure to direct sunlight.

*Statistical Analysis*

An *a priori* sample size calculation was not conducted as this was an exploratory study. All hypotheses were tested at alpha = 0.05, and 2-sided p-values ≤ 0.05 were considered statistically significant.

Descriptive statistics (number of subjects, mean, standard error of the mean) were presented by intervention for pre-dose, post-dose and for differences, as appropriate. Differences between interventions were assessed by repeated measures analysis of variance (ANOVA). Within group differences were assessed by paired t-test or Wilcoxon signed rank test, depending on the data distribution. All analyses were performed using SAS for Windows version 9.3 (Cary, NC).

## Results

*Subjects*

Twenty-four eligible and consenting participants (mean age 26.50 ± 0.99 years; BMI 25.31 ± 0.51 kg/m$^2$) were randomized equally in a 1:1 ratio to either the ASI → placebo or placebo → ASI sequence (Figure 2). Prior to enrollment, participants reported completing a mean of 35.6 ± 5.9 minutes of exercise per week, with the majority of participants (66.7%) completing between 15 and 75 minutes. All participants were deemed healthy by the Qualified Investigator (QI) as per the assessment of anthropometrics and vital signs (Table 1), hematology, clinical chemistry and physical examination. Participant demographic information is presented in Table 1. The Intent-to-Treat (ITT) population comprised of all 24 participants who received either study product and for whom post-randomization information was available. A total of 2 participants in the ASI→placebo arm dropped out of the study for reasons not related to the study.

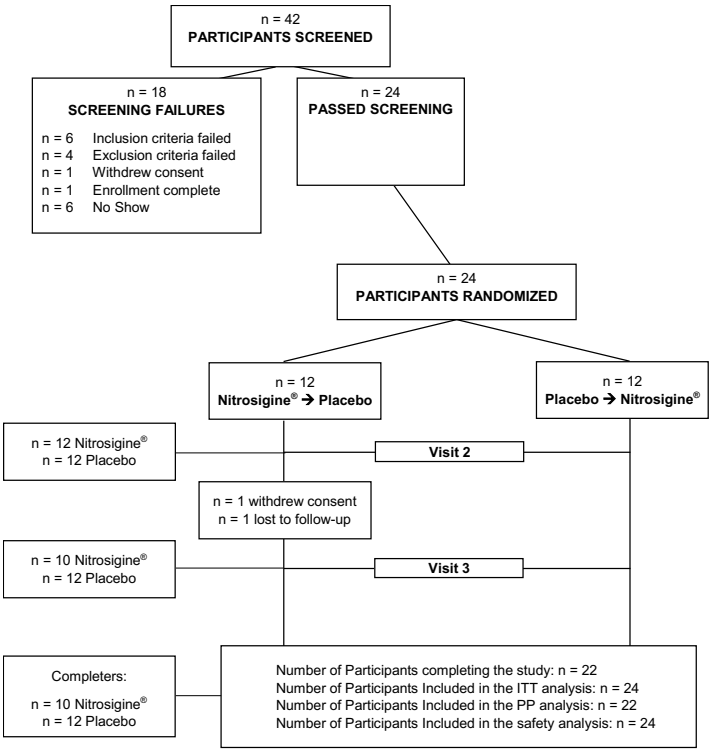


Figure 2. Participant disposition: Of the 42 participants screened, 24 eligible were enrolled and were randomized to receive either ASI (Nitrosigine®) or placebo with 12 per sequence. At Visit 3, participants crossed over and consumed the other product. Two participants, both early terminations, were not included in the per protocol population. (ITT, intention to treat; PP, per protocol).

Table 1. Baseline demographic and clinical characteristics of all participants enrolled (n=24)

| Parameter<br>Mean +/- SEM | All participants (n=24) |
|---|---|
| **Age** (years) | 26.50 ± 0.99 |
| **Weight** (kg) | 80.08 ± 2.08 |

| Parameter<br>Mean +/- SEM | All participants<br>(n=24) |
|---|---|
| **BMI** (kg/m$^2$) | 25.31 ± 0.51 |
| **Left Systolic Blood Pressure** (mmHg) | 117.60 ± 1.97 |
| **Left Diastolic Blood Pressure** (mmHg) | 73.97 ± 1.69 |
| **Right Systolic Blood Pressure** (mmHg) | 120.28 ± 2.01 |
| **Right Diastolic Blood Pressure** (mmHg) | 74.28 ± 1.48 |
| **Heart Rate** (bpm) | 75.85 ± 1.91 |

*Cognitive function: Trail Making Test (TMT) Part A and B*

Following the mGXT, time to complete TMT A was reduced by 2.80 ± 5.97 seconds (-5%) with ASI compared to a 19.82 ± 4.58 second increase (+51%) with placebo (p = 0.01 between interventions) (Figure 3, Table 2). A similar trend was observed in the change from pre-dose in TMT B completion between interventions (p = 0.05). There was a decrease of 5.54 ± 3.77 seconds (-7%) with ASI versus an increase of 7.68 ± 5.06 seconds (+11%) with placebo (Figure 3).

Table 2. Cognitive function measured as mean time (s) to complete Trail Making Test (TMT) before and after a mGXT pre- and post-consumption of ASI or placebo.

| Trail Making Test (s) | | | |
|---|---|---|---|
| **Time Point** | **ASI (Nitrosigine®)<br>Mean ± SEM (n)<br>within Group P-Value+** | **Placebo<br>Mean ± SEM (n)<br>within Group P-Value+** | **Between Group<br>P-Value*** |
| | **Part A** | | |
| Pre-Dose | 57.58 ± 5.78 (24) | 39.05 ± 4.26 (22) | |
| Post-Dose | 54.79 ± 3.21 (24) | 58.86 ± 3.89 (22) | |
| Change from Pre- to Post-Dose | -2.80 ± 5.97 (24)<br>p = 0.644 | 19.82 ± 4.58 (22)<br>p ≤ 0.001+ | 0.007* |
| | **Part B** | | |
| Pre-Dose | 82.25 ± 6.12 (24) | 72.45 ± 5.59 (22) | |
| Post-Dose | 76.71 ± 5.30 (24) | 80.14 ± 5.98 (22) | |
| Change from Pre- to Post-Dose | -5.54 ± 3.77 (24)<br>p = 0.155 | 7.68 ± 5.06 (22)<br>p = 0.144 | 0.050* |

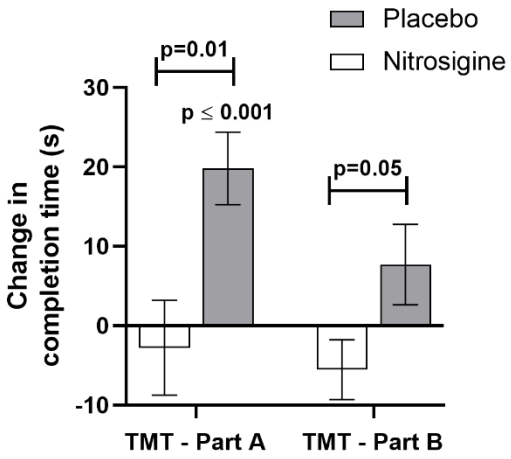


Figure 3. Mean change in Trail Making Test (TMT) Parts A and B completion time (s) from baseline to post-exercise with ASI (Nitrosigine®) or placebo. Values are mean ± SEM (n = 24). P-values between bars refer to a difference between interventions and p-values above bars refer to a within-group difference from baseline.

*Safety outcomes*

There were no significant differences between the effect of ASI versus placebo on the safety outcomes pre- and post-supplementation (data not shown), except for a greater reduction in potassium concentration ($p = 0.04$) and an increase in lymphocyte count ($p = 0.04$) with ASI. There was a greater reduction in mean corpuscular hemoglobin levels when participants took placebo. However, all values remained within normal clinical ranges and all participants were deemed healthy as per the QI. ASI did not exert a significant effect on the change in mean arterial pressure (MAP; $p = 0.581$), systolic blood pressure (SBP) or heart rate pre- to post-supplementation compared to placebo. Participants in the ITT group, but not the PP group, showed a significant increase in MAP and SBP from pre-supplementation to post-supplementation ($p \leq 0.01$ for both interventions). These changes were deemed to be not clinically significant by the QI.

**Discussion**

This randomized, double-blind, placebo-controlled crossover study in healthy, recreationally active males showed significant improvements by ASI, a highly bioavailable and active form of arginine, in post-exercise cognitive function tests compared to placebo. These data support acute ASI supplementation to enhance cognitive function associated with intense physical activity.

Results of the current study revealed that acute supplementation with ASI elicits a significant improvement in cognitive function as assessed by the TMT, which evaluates motor speed and visual attention. TMT Parts A and B are different in their symbolic complexity, spatial arrangement, and cognitive demands [26,27]. Intense exercise led to a significant decrease in cognitive performance in recreationally active males. Following the mGXT, participants in the placebo group had significantly worse performance on Part A of the TMT than pre-exercise. Part A is a measure for visuo-perceptual abilities while Part B assesses cognitive flexibility and executive function[24,28]. Supplements that enhance mental focus and cognitive function may lead to greater training adaptations and long-term performance improvements in athletes[29,30]. In the current study population, acute ASI supplementation was shown to improve cognitive function following exercise, which may also enhance sport performance in this population.

At all competition levels, sports performance requires participants to anticipate and react continuously in a changing, and relatively unpredictable situation. Success in sports does not rest solely on physical capability, as there is a major cognitive component based on how information is processed given the complex and quickly changing contexts in a game or event[1,31]. The importance of cognition on physical performance is supported by research demonstrating that when subjects are mentally fatigued their ratings of perceived exhaustion during exercise are significantly increased, while their time of engagement in physical activity and time to reach maximal level of perceived exertion is reduced compared to controls[5]. Moreover, certain types of physical activities, such as active treadmill exercise, have been shown to reduce cognitive performance during exercise[6]. Notably, TMT B scores have been linked with improved athletic performance[24,25]. The ability of ASI to reduce TMT B completion time post-exercise in this study highlights its potential as a pre-workout supplement to enhance cognitive function during or after exercise. In the present study, ASI significantly reduced time to complete the TMT A test by 5% and time to complete TMT B by 7%. Pre-supplement TMT completion times were similar

to those previously reported, which also showed a greater reduction in TMT completion time 3 and 14 days after ASI supplementation without exercise[14]. These results support the previous findings that certain types and instances of intense exercise can negatively affect cognitive function. The ability of ASI to prevent exercise-induced mental fatigue could have profound effects on recreational athletes and physically active individuals who suffer from mental fatigue during extended amounts of exercise. To our knowledge, arginine supplementation and cognitive evaluation via the TMT test has not been examined in the context of exercise, except for Kalman et al. (2016) where pre-exercise ASI supplementation was shown to improve cognitive function[32]. Such an improvement in mental focus and acuity with a single dose of ASI suggests future work investigating a role for ASI in cognitive enhancement in athletics deserves further investigation[14].

No safety concerns were raised with acute ASI consumption, all clinical chemistry, hematology, vital signs, and anthropometric measurements remained within the clinical range, and no severe adverse events were observed. A limitation of the study is that only males were included, therefore possible gender differences could not be evaluated. Future studies can be of longer duration to assess chronic effects of ASI on cognitive performance associated with physical exercise.

The current study examined the effects of a single dose of ASI on cognitive function following intense exercise. Acute ASI consumption significantly improved cognitive functioning as assessed by the TMT A and B tests, which measured visuo-perceptual abilities, cognitive flexibility, and executive function. While long-term exercise can benefit cognitive performance, individuals also report that strenuous exercise can cause acute mental fatigue and cognitive impairments. This study highlights a role for ASI as a pre-workout supplement to enhance cognitive performance associated with physical activities. via augmentation of cognitive function is an emerging area of research.

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