The Safety of Chronic Creatine Nitrate Supplementation: A Twenty Eight Day Evaluation

Matt M. Mosman, Paul H. Falcone, Laura R. Carson, Chih-Yin Tai, Jordan M. Joy, Michael P. Kim, Jordan R. Moon

ABSTRACT

The ergogenic effects of creatine monohydrate (CM) has made it one of the most widely used supplements in various populations. It is estimated that 28-41% of NCAA athletes are using CM in 17 different sports while 29-57% (military vs civilian) of health club members use CM. The safety of CM on blood chemistry and hematology values has been well established. However, little is known about the impact of various other forms of creatine on safety parameters, specifically creatine nitrate (CN). **PURPOSE**: To determine the safety of ingesting a CN supplement for 28 days. **METHODS**: Twenty men between the ages of 18 and 31 participated in the study. Subjects were instructed to report to the blood testing facility in an 8 hour fasted, euhydrated state and not to exercise the morning of testing. Subjects then provided a baseline blood and urine sample for full safety panels (for a full list of variables, see table 1), height, weight, blood pressure, and heart rate. Subjects were divided into two groups: group A (n =10) was instructed to consume 1g daily of CN, while group B (n = 10) was instructed to consume 2g daily for 28 days. After baseline measurements were completed subjects were provided with the CN supplement and instructed to record a supplementation and adverse events log for 28 days. They were also instructed to maintain their current diet and exercise routine as it had been for at least two months prior to the start of the study. At the conclusion of the 28 day supplementation period, subjects were instructed to return to the blood testing facility in an identical state to baseline testing to provide a blood and urine sample, height, weight, blood pressure, and heart rate. **RESULTS**: Over the 28 day CN supplementation period no statistically or clinically significant changes in blood chemistry or hematology were observed. No adverse events were reported in this study. **CONCLUSIONS:** Chronic CN supplementation appears to be safe in male populations when taken within recommended usage guidelines. **PRACTICAL APPLICATIONS:** CN supplementation appears to be a safe alternative to CM in male populations. As an ergogenic aid CN may be as effective as CM in producing greater strength and fat-free mass development; however more studies comparing CN to CM are needed to confirm this theory.

INTRODUCTION

Creatine (Cr) is an amino acid-derived compound that is utilized in the body to fuel high intensity exercise of short duration. Cr is produced in limited quantities endogenously in the liver, kidneys, and pancreas, but is also commonly taken as a dietary supplement, ingested in the form of creatine monohydrate (CM). The effects of CM as a nutrition supplement have been widely studied as they relate to sports performance and muscular fitness.[1] Use of CM has been associated with increases in muscular strength, endurance, and improvements in body composition.[2] Moreover, the safety of CM has been indicated by a lack of evidence of adverse events following either short-term or long-term CM supplementation [3]. As a result, CM has become one of the most commonly used performance supplements among athletes and recreational users alike.[4].

Initially, CM was thought to be the only readily available and effective compound for Cr supplementation; however with the discovery of alternative forms of Cr bonds there now exists a wealth of Cr formulations manufactured by supplement companies. Creatine Nitrate (CN) is one of these alternative forms which can be classified as a creatine salt. Due to Cr being a weak base it must be paired with a compound strong enough to form a strong acid in order to form a salt. By doing this the strong acid that is formed will in turn decrease the pH of the solution, which in turn increases the solubility of Cr.[4] Therefore a creatine salt such as CN could potentially have a higher solubility than CM, thus the value in more studies involving CN and its safety.

Due to the wide consumption and use of Cr as a nutritional supplement, the validation of safety is crucial towards CN as a viable alternative to CM amongst athletes and manufacturers. The primary concerns when supplementing with Cr are effects on the kidneys, as well as increased risk of dehydration and cramping.[4] Such factors need to be tested in order to reduce possible negative side effects when using a creatine salt based compound such as CN. Therefore the goal of this study was to determine such safety of ingesting a CN supplement for 28 days, and the safety parameters that should be considered.

METHODS

Participants

Twenty recreationally trained males participated in this study. Subjects were required to be apparently healthy and free from disease, have no physical condition that was considered a contraindication to cardiovascular training, and abstain from smoking, alcohol, and anti-inflammatories during the 28 day period. In addition, all subjects were required to engage in physical activity at least 2 days per week. Subjects indicated participation in one or more of the following physical activities: resistance training, running, walking, basketball, soccer, crossfit, and rugby. Prior to testing, the study was approved by the MusclePharm Institutional Review Board for use of human subjects, and all subjects provided written informed consent to participate in the study.

Study Design

All subjects were randomly divided into two groups. Group A was instructed to ingest one serving while Group B was instructed to consume 2 servings of the CN every day for 28 days. Subjects were not required to consume the CN prior to exercise, and Group B was permitted to consume one serving twice daily. The CN (Iron Cre3^{TM}, MusclePharm Corp., Denver, CO) contained 1000mg of creatine nitrate per serving.

Prior to the supplementation period, subjects were instructed to report to a local blood testing facility (Laboratory Corporation of America, Denver, CO, USA) in an 8 hour fasted, euhydrated state and not to exercise the morning of testing. Each subject completed an informed consent, health history, and exercise questionnaire. Resting heart rate and blood pressure was taken using an automated blood pressure cuff. The average of two tests with 2 minutes between tests was recorded and used for analysis. Height and weight was measured using a SECA 703 high capacity column scale. Subjects then provided a baseline blood and urine sample for full safety panels.

After baseline measurements were completed, subjects were provided with the CN supplement and instructed to record a supplementation and adverse events log for 28 days. They were also instructed to maintain and record their current diet and exercise routine as it had been for at least two months prior to the start of the study. Maintenance of diet was monitored using 3 day food logs for each week. At the conclusion of the 28 day supplementation period, subjects were instructed to return to the blood testing facility in an identical state to baseline testing to provide a post blood and urine sample, height, weight, blood pressure, and heart rate. Supplementation, food, exercise, and adverse event logs were also collected at this time.

Blood Draws/Urinalysis

All blood (taken via venipuncture by a trained phlebotomist) and urine samples were done at a local diagnostic laboratory (Laboratory Corporation of America, Denver, CO, USA). Pre supplementation samples were taken with the subject in an 8 hour fasted, euhydrated state while post samples were taken in an identical state one day after ceasing supplementation and at the same time of day as pre supplementation blood and urine samples. Variables recorded from the blood and urine analysis consisted of white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW), platelets (percent and absolute), neutrophils (percent and absolute), lymphocytes (percent and absolute), monocytes (percent and absolute), eosinophils (percent and absolute), basophils (percent and absolute), serum glucose, blood urea nitrogen (BUN), creatinine, eGFR, BUN:creatinine, sodium, potassium, chloride, carbon dioxide, calcium, protein, albumin, globulin, albumin:globulin ratio (A/G ratio, bilirubin), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT)., total cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), ammonia, urine specific gravity, pH, and urobilinogen.

Subject Characteristics

	n	Age	Height	Weight
All	20	25 ± 4	180 ± 7	88.7 ± 13.3
Group A	10	26 ± 5	180 ± 8	86.9 ± 14.1
Group B	10	24 ± 4	180 ± 7	90.3 ± 13.2

RESULTS

Table 1	Single (A)					Double (B)				
	Pre	SD	Post	SD	p value	Pre	SD	Post	SD	p value
weight	191.23	30.87	192.70	31.04	0.21	198.58	28.93	200.54	26.75	0.30
systolic average	119.50	14.01	120.83	17.13	0.68	126.68	11.17	130.50	4.71	0.25
diastolic average	76.06	10.33	74.89	14.27	0.69	79.09	9.73	77.41	8.69	0.67
pulse average	64.94	9.87	68.17	10.38	0.12	65.50	10.67	65.32	11.84	0.94
WBC	5.38	1.21	6.24	1.84	0.16	5.97	0.93	5.96	0.90	0.96
RBC	5.22	0.10	5.15	0.24	0.23	5.19	0.19	5.26	0.18	0.18
Hemo	16.09	0.62	15.76	0.97	0.15	15.53	0.56	15.86	0.47	0.17
Hema	47.77	1.80	47.12	2.34	0.21	45.64	1.56	46.60	1.23	0.09
Glu	90.44	9.45	89.78	5.54	0.74	85.36	3.85	87.91	6.47	0.12
BUN	19.44	4.13	18.11	6.47	0.42	17.82	3.63	19.91	2.12	0.07
Cr	1.10	0.10	1.09	0.14	0.70	1.21	0.18	1.23	0.15	0.64
BUN/Cr Ratio	17.56	3.68	16.78	6.06	0.53	14.64	2.29	16.18	1.94	0.08
Sodium	137.11	1.36	137.78	2.22	0.43	138.64	2.06	125.40	41.19	0.31
Pot	4.01	0.30	4.08	0.24	0.33	4.09	0.27	4.11	0.25	0.86
AST	33.11	10.52	33.22	9.42	0.97	32.45	15.67	28.55	7.03	0.42
ALT	31.00	8.29	35.89	12.79	0.28	24.45	6.25	23.82	4.96	0.77
Total Chol	154.78	40.18	151.11	28.41	0.69	155.09	24.64	164.18	28.73	0.19
Tri	114.22	95.23	106.11	69.91	0.73	80.55	22.83	85.18	24.94	0.56
HDL	48.22	12.17	37.44	16.69	0.12	55.36	14.55	55.64	12.82	0.88
LDL	83.89	25.90	92.56	23.40	0.40	83.55	25.20	91.45	26.15	0.20
Ammonia	39.33	13.44	42.11	20.08	0.63	38.50	6.42	51.80	22.86	0.09
SG	1.01	0.01	1.01	0.01	0.78	1.02	0.01	1.02	0.01	0.20
Ph	6.44	0.63	6.61	0.65	0.44	6.23	0.47	6.23	0.34	1.00
Protein	1.00	0.00	1.00	0.00	N/A	1.00	0.00	1.00	0.00	N/A
Glucose	1.00	0.00	1.00	0.00	N/A	1.00	0.00	1.00	0.00	N/A
Ketones	1.00	0.00	1.00	0.00	N/A	1.00	0.00	1.09	0.30	0.34
Bilirubin	1.00	0.00	1.00	0.00	N/A	1.00	0.00	1.00	0.00	N/A
Urobilinogen	0.20	0.00	0.20	0.00	N/A	0.20	0.00	0.20	0.00	N/A
Nitrite	1.00	0.00	1.00	0.00	N/A	1.00	0.00	1.00	0.00	N/A

CONCLUSIONS

Chronic supplementation of the CN did not affect kidney or liver enzymes or cholesterol values. No interactions were observed and no mean difference from pre to post was observed for either group for all fasted blood markers ($P > 0.05$). Therefore chronic CN supplementation appears to be safe in male populations when taken within recommended usage guidelines.

PRACTICAL APPLICATIONS

CN supplementation appears to be a safe alternative to CM in male populations. As an ergogenic aid CN may be as effective as CM in producing greater strength and fat-free mass development; however more studies comparing CN to CM are needed to confirm this theory.

REFERENCES

1. Buford T, Kreider R, Stout J, Greenwood M, Campbell B, Spano M, Ziegenfuss T, Lopez H, Landis J, Antonio J. International Society of Sports Nutrition position stand: creatine supplementation and exercise.J Int Soc Sports Nutr. 2007;4:6. doi: 10.1186/1550-2783-4-6

2. American College of Sport Medicine. Round Table, the physiological and health effects of oral creatine supplementation. Med Sci Sports Exc. 2000;32:706–717.

3. Kim, H., Kim, C., A. Carpentier, & Poortmans, J. R. (2010). Studies on the safety of creatine supplementation. Amino Acids, 40(5), 1409-1418. doi:10.1007/s00726-011-0878-2

4. Wells, S., & Esgro, B. (2013). Creatine. In *Sports nutrition and performance enhancing supplements* (pp. 165-200). Ronkonkoma, NY: Linus Learning.