Journal of Kerman University of Medical Sciences

JKMU

Journal of Kerman University of Medical Sciences, 2020; 27 (3): 213-221

Evaluation of L-arginine Effects on Refractory Seizures in Epileptic Patients

Hossein Ali Ebrahimi Meimand, M.D.[1], Farhad Iranmanesh, M.D.[2], Mahdi Ansari, Ph.D.[3], Hasibeh Molla Mohammadi, [4], Sepideh Ebrahimi, [4]

1- Professor of Neurology, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran (Corresponding author; E-mail: hebrahimi@kmu.ac.ir)

2- Professor of Neurology, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran

3- Professor of Pharmacology, Kerman University of Medical Sciences, Kerman, Iran

4- Medical Student, Afzalipour School of Medicine, Kerman University of Medical Sciences, Kerman, Iran

Received: 30 June, 2019 Accepted: 6 April, 2020

ARTICLE INFO

Article type:
Original Article

Keywords:
L-arginine
Refractory epilepsy
Epilepsy
Ketogenic diets

Abstract

Background: epilepsy is one of the common neurological disorders and approximately 0.5-1% of populations suffers from it. Unfortunately, despite of treatment by antiepileptic drugs, between 20-30% of patients cannot be controlled completely. There are a lot of supplementary therapies for this group of patients and in this study, L-arginine was used as an additional therapy in refractory epileptic patients.

Methods: Two groups of epileptic patients (n=21) were selected randomly. Group 1 received lactose as a placebo, and group 2 received L-arginine (twofold of daily need) as a drug for three months. We used a standard questionnaire for evaluating the effect of L-arginine on the quality of life before and after the study.

Results: we did not find significant change in the quality of life of patients after using L-arginine, but the epileptic attacks decreased in L-arginine group significantly.

Conclusion: L-arginine therapy is safe and can decrease the rate of seizure attacks in refractory epileptic patients, and can be an alternative of ketogenic diets.

Citation: Ebrahimi Meimand H.A, Iranmanesh F, Ansari M, Molla Mohammadi H, Ebrahimi S. Evaluation of L-arginine Effects on Refractory Seizures in Epileptic Patients. *Journal of Kerman University of Medical Sciences*, 2020; 27 (3): 213-221.

Introduction

Epilepsy is a common neurological disorder characterized by recurring seizure. Approximately, 50-70 million people live with epilepsy worldwide. In other words, approximately 1% of the world population has epilepsy and it is the second common neurologic disorder after stroke (1-3).

The prevalence of epilepsy in developing countries is higher than that in the developed countries, but according to a study in Iran, the point prevalence of active epilepsy is 7.78/1000 (4) which is similar to that in developed countries.

Lifelong seizure freedom without adverse effects can be considered the most clinically relevant outcome of any intervention for epilepsy (5). Unfortunately, despite of treatment by antiepileptic drugs, between 20-30% of patients cannot be controlled well (6-7). Drug resistant epilepsy (refractory epilepsy) may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to

achieve sustained seizure freedom (8). Refractory epilepsy can significantly affect life. Patients with refractory epilepsy may have trouble at work or school and are always worry about their next seizure. They may also have injuries resulted from their seizures.

Epileptic patients, especially the patients who are not under good control, are at risk of a lot of problems; for example, sudden unexplained death (SUDEP) is one of the major risks in epilepsy, especially in generalized tonic-clonic (GTC) epilepsy and it has been found in a systematic review that people with 3 or more GTC per year are at a 15-fold increased risk of SUDEP (9).

In pregnant women with epilepsy, seizure attacks are a major challenge, and the next challenge is use of anti-epileptic drugs. About 1% of the pregnant women have epilepsy (10).

In the treatment of epilepsy, supplement therapy may be effective in reducing some problems such as stress, sleep disorders and stimulating factors (11).

Among the challenging issues is the diet and different views have been reported in terms of the efficacy and positive or negative effects of certain foods. Ketogenic diet has long been proposed and used by the medically resistant patients for many years. Atkins diet, which leads to ketosis, has also received attention. Consumption of foods containing protein chains has been proposed as well (12-15).

A study on rat showed that chargeable amino acids can delay and decrease the convulsion induced by intra peritoneal injection of penthylentetrazol (16).

Administration of charged amino acids, arginine, and glutamic acid can decrease seizure attacks in patients suffering from uncontrolled epilepsy (17).

Arginine regulation is a subject of the extent of oral use and its internal production; hence, arginine needs to be viewed as a semi-essential amino acid. The short-term treatment outcome of this novel L-arginine supplementation therapy in Pyridoxine-dependent epilepsy was successful for biochemical and neurocognitive improvements (18).

Results of animal and human studies show that L-arginine metabolism has diverse effects on human physiology. Collectively, the data suggest that arginine supplementation is a safe and generally well-tolerated nutraceutical that may improve metabolic profiles in humans (19, 20).

The ultimate metabolism of arginine leads to three substances of nitrous oxide, agmatine (AGM), and glutamic acid. Agmatine, a product of arginine decarboxylation, influences multiple physiologic and metabolic functions. The findings suggest that AGM elevates the synthesis and level of cAMP, thereby mimics the effects of caloric restriction with respect to metabolic reprogramming. The effects of injected AGM in animals include anticonvulsant, anti-neuro-toxic, and antidepressant-like actions. AGM has neuroprotective effects too. Decreased arginine level or bioavailability has a role in pathogenesis of some disorders, and an attention has been directed to arginine therapy (21-24).

This study evaluated the effect oral L-arginine as a supplementary therapy in refractory epileptic patients.

Material and Methods

This double- blind clinical trial was done on refractory epileptic patients treated by two anti-epileptic drugs (increasing dosage until the appearance of side effects) with duration of at least one year, and with at least one epileptic attack per month.

The patients were randomly divided into the two groups (drug and placebo). Three months before beginning L-arginine or lactose as the placebo [the most common symptoms of

lactose intolerance included audible bowel sounds, abdominal pain and meteorism, that occurred after consuming 25 g of lactose (25)], the epileptic attacks were recorded by patients or their caregivers. Although L-arginine does not have important side effects, its effects on life of patients were evaluated by using the questionnaire of quality of life in epilepsy-31 version 1.0 (26). The questionnaire was completed before the beginning of the project.

The L-arginine supplement prepared by Caren corporation was administered orally at a twofold of daily need dose (daily need for adults 6 gr for three months) and placebo was administered too (27). The attacks in this duration were recorded. At the end of study, the questionnaire of quality of life was completed again.

The exclusion criteria were pregnancy, other disease (hypertension, diabetes,…), non-epileptic neurologic disorder, hyper-sensitivity to Arginine supplement or incorporation and use of anti-platelet, anticoagulant drugs. All patients or their caregivers signed a consent form. Demographic information and other findings were analyzed using independent t-test, chi square test and logistic regression. The present study was approved by the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.REC 1396-1920) and IRCT under number IRCT201603078436N3.

Results

This double blind clinical trial was done on 42 refractory epileptic patients (21 cases in lactose, as a placebo, group and 21 cases in L-arginine group). At first, 52 patients were selected of whom, one case was excluded due to the hyper activity, one patient was excluded due to having other disorder, and 8 cases were excluded because of noncooperation. The two groups showed no significant difference in mean age (25.9±14.9 vs. 24.3±13.9 years) and other variables including education, marital status and job (P>0.05).

Before the intervention, the two groups showed no significant difference in terms of their past 4 weeks feelings (muscular strength, nervousness, unhappiness, calmness, loss of energy, downheartedness, exhaustiveness, happiness, tiredness, worry about another seizure) and having any difficulty or social activity limitation (P>0.05), the quality of life (P=0.697), memory, remembering, concentration and activities (P>0.05), and health state (P=0.7). The number of seizure attacks in placebo group was more than that in the L-arginine group but, the difference was not significant (P=0.07).

As it is seen in table 1, in the L-arginine group, the rate of epileptic attacks decreased significantly (P=0.000).

The quality of life and health state, in spite of being increased in the L-arginine group, did not show significant difference between the two groups (Table 2).

After the intervention, subjects' feelings did not show significant difference, except for nervousness which significantly increased in the L-arginine group (Table 3).

Some important items such as memory, remembering, concentration and some activities did not show significant changes after the intervention in spite of increase seen in some of them (Tables 4& 5).

Table 1. Comparison of the rate of seizure attacks before and after the intervention in the two groups

Mean number of attacks / Group	Before	after	P value
Placebo	15±3.7	21 ± 5	0.075
L-arginine	11±3.6	3±1	0.000

Odd ratio # 4 for L-arginine

Table 2. Comparison of the two groups in terms of quality of life (overall) and health state after the intervention

	group	Mean	Std. Deviation	P value
Quality of life	PLACEBO	5.5000	2.52357	
	L-ARGININE	6.2105	2.74021	0.697
Health state	PLACEBO	46.5000	26.01113	
	L-ARGININE	59.4737	24.60210	0.480

Table 3. Comparison of the two groups in terms of subjects' feelings during the 4-week follow up period

feelings	Group	Mean	Std. Deviation	P value
feeling active	PLACEBO	3.6500	1.59852	
	L-ARGININE	3.3158	1.52944	0.894
nervousness	PLACEBO	2.6500	1.46089	
	L-ARGININE	3.3684	.95513	0.043
unhappiness	PLACEBO	3.2500	1.61815	
	L-ARGININE	3.8947	1.76052	0.539
calmness	PLACEBO	3.6500	1.69442	
	L-ARGININE	3.2632	1.44692	0.346
feeling energized	PLACEBO	3.2500	1.48235	
	L-ARGININE	3.7895	1.43678	0.720
feeling blue	PLACEBO	3.6000	1.63514	
	L-ARGININE	3.3684	1.70654	0.700
exhaustiveness	PLACEBO	3.1500	1.87153	
	L-ARGININE	3.9474	1.64903	0.380
happiness	PLACEBO	4.4000	1.66702	
	L-ARGININE	3.5263	1.54087	0.919
tiredness	PLACEBO	3.5000	1.84961	
	L-ARGININE	3.8421	1.34425	0.043
Worry about next seizure	PLACEBO	3.6500	1.75544	
	L-ARGININE	3.7368	1.62761	0.668
Problem solving	PLACEBO	4.1000	2.46875	
	L-ARGININE	3.9474	1.54466	0.342
Social activity	PLACEBO	3.4000	1.75919	
	L-ARGININE	3.3684	1.73879	0.946

Table 4. Comparison of the two groups in terms of unrest feeling and memory and concentration problems after the intervention

Problems	Group	Mean	Std. Deviation	P value
feeling of unrest	PLACEBO	2.3500	.93330	
	L-ARGININE	2.6842	1.20428	0.74
memory problems	PLACEBO	2.9500	1.27630	
	L-ARGININE	3.0000	1.33333	0.619
concentration	PLACEBO	3.8000	1.43637	
problems	L-ARGININE	3.6316	1.53516	0.556
Problem in doing activities	PLACEBO	3.6000	1.18766	
	L-ARGININE	3.9474	1.64903	0.061

Table 5. Comparison of the two groups in terms of problems with certain activities after the intervention

	Group	Mean	Std. Deviation	P value
Leisure	PLACEBO	3.2000	1.00525	
	L-ARGININE	3.7895	.97633	0.947
Driving	PLACEBO	3.2500	1.37171	
	L-ARGININE	4.2632	1.28418	0.387
Fear of seizure	PLACEBO	1.9500	.99868	
	L-ARGININE	2.2105	.85498	0.487
self-hurting	PLACEBO	2.0500	.94451	
	L-ARGININE	2.2632	1.14708	0.149
Social problems	PLACEBO	2.1000	1.07115	
	L-ARGININE	2.3684	1.11607	0.845
Medicine bad	PLACEBO	2.3500	1.30888	
	L-ARGININE	2.6842	1.37649	0.758

Discussion

Refractory seizure is one of the most challenging issues in epilepsy. In this study, we evaluated the effect of L-arginine in these patients, and the obtained data showed decrease of epileptic attacks (table 1). This effect might be due to the compensation of polarization in epileptic neurons, and it suggests that the ketogenic or Atkins diets can be effective too. It can be proposed that decreased NO bioavailability happens in epileptic neuron, as it has been reported in asthma (28, 29).

Nitric oxide (NO) is produced from arginine (30). Arginine is a basic amino acid, and in studies from 1950 to 1970, it has been considered as a nonessential amino acid for the health of adults (31), but an essential amino acid for the growth of human beings and animals (32, 33). However, in diseases, as well as physical traumas, it turns into an essential amino acid (34). The sources of free arginine within the body are dietary protein, endogenous synthesis, and turnover of body proteins (35, 36). Arginine accumulates in astroglial cells for the benefit of

neighboring cells in need of the amino acid for a proper synthesis of NO (36).

There are a few studies proving the effect of L-arginine on seizures (37-39).

In this study, L-arginine did not have any effect on the overall quality of life and health state of patients.

L-arginine could improve patients' feelings, but without significant differences (P> 0.05), except for nervousness which increased significantly, but tiredness decreased significantly (P=0.04, table 3). According to some studies, arginine-based supplements can be used on an acute basis for delaying the onset of neuromuscular fatigue (40, 41).

L-arginine did not have any effect on memory and remembering, but showed beneficial effect on concentration and on doing one thing at a time, but not significantly (P=0.06, table 4). L-arginine did not change special activities such as leisure state, driving, fear of seizure and fear of self-hurting during seizure attack, social problems and physical effects of medication (table 5).

Since L-arginine do not have important side effects on patients, it can be safely used in epileptic patients. The toleration of L-arginine is very better than that of ketogenic and Atkin's diets.

Conclusion

In refractory epileptic patients, L-arginine therapy is safe and can decrease the rate of seizure attacks. L-arginine therapy can be considered as an alternative to ketogenic and Atkins diets for patients with refractory or uncontrollable seizures.

Acknowledgement

This study was approved by Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran and is a part of Hasibeh Molla Mhammadii (medical student) M.D. thesis.

References

1. Scott RA, Lhatoo SD, Sander JW. The treatment of epilepsy in developing countries: where do we go from here?Bull World Health Organ 2001; 79(4): 344-51.
2. Banerjee PN, Filippi D, Hauser WA. The descriptive epidemiology of epilepsy-a reviewEpilepsy Res 2009; 85(1): 31–45. DOI: 10.1016/j.eplepsyres.2009.03.003.
3. Sayehmiri K, Tavan H, Sayehmiri F, Mohamadi I, Carson KV. Prevalence of Epilepsy in Iran: A Meta-Analysis and Systematic Review. Iran J Child Neurol 2014; 8(4):9–17
4. Ebrahimi H, Shafa M, Hakimzadeh Asl S, Prevalence of Active Epilepsy in Kerman, Iran: a House Based Survey. Acta Neurol Taiwan 2012; 21(3): 115-24.
5. Sillanpää M, Haataja L, Shinnar S. (2004) Perceived impact of childhood-onset epilepsy on quality of life as an adult. Epilepsia 45: 971– 977
6. K. Radhakrishnan and M. B. Rao, in Epilepsy in India, B. S.Singhal and D. Nag, Eds 2000; pp. 343–362.

7. Devinsky O. Patients with Refractory Seizures. N Engl J Med 1999; 340(20): 1565-70. DOI: 10.1056/NEJM199905203402008

8. Patrick Kwan, Alexis Arzimanoglou, Anne T. Berg, Martin J. Brodie, W. Allen Hauser, Gary Mathern, Solomon L. Moshé, Emilio Perucca,Jacqueline French. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia Volume51, Issue6, June 2010, Pages 1069-1077

9. Surges R, Sander JW. Sudden unexpected death in epilepsy: mechanisms, prevalence, and prevention. Curr Opin Neurol 2012; 25(2): 201-7. DOI: 10.1097/WCO.0b013e3283506714.

10. Ebrahimi H, Arabpour E, Shafeie K, Khanjani N. Evaluation of seizures in pregnant women in Kerman – Iran. World Family Medicine 2017; 15(8): 52-58. DOI 10.5742/MEWFM.2017.93056.

11. Parra J, Kalitzin SN, Lopes da Silva FH. Photosensitivity and visually induced seizures. Curr Opin Neurol 2005; 18(2):155-159. DOI: 10.1097/01.wco.0000162857.52520.68.

12. Peuscher R, Dijsselhof ME, Abeling NG, Van Rijn M, Van Spronsen FJ, Bosch AM. The Ketogenic Diet Is Well Tolerated and Can Be Effective in Patients with ArgininosuccinateLyase Deficiency and Refractory Epilepsy. JIMD Rep 2012; 5: 127-130. DOI: 10.1007/8904_2011_115.

13. Nei M, Ngo LY, Sirven JI, Sperling MR. Ketogenic diet in adolescents and adults with epilepsy. Seizure 2014; 23(6): 439-42. DOI: 10.1016/j.seizure.2014.02.015.

14. Xiao Y, Li X. Polyunsaturated fatty acids modify mouse hippocampal neuronal excitability during excitotoxic or convulsant stimulation. Brain Res 1999; 846(1): 112-21. DOI: 10.1016/s0006-8993(99)01997-6.

15. Kossoff EH, Krauss GL, McGrogan JR, Freeman JM. Efficacy of the Atkins diet as therapy for intractable epilepsy Neurology 2003; 61(12):1789-91. DOI: 10.1212/01.wnl.0000098889.35155.72.

16. Ebrahimi HA, Asadi M, Effect of charged amino acids on convulsion due to penthylentetrazol in male adult rat. Iranian journal of neurology 2005; 4(12): 13-7.

17. Ebrahimi HA, Ebrahimi S. Evaluation of the Effects of Charged Amino Acids on Uncontrolled Seizures. Neurol Res Int 2015; 2015: 124507. DOI: 10.1155/2015/124507.

18. Mercimek-Mahmutoglu S, Cordeiro D, Cruz V, Hyland K. Struys EA, Kyriakopoulou L, etal. Novel therapy for pyridoxine dependent epilepsy due to ALDH7A1 genetic defect: l-arginine supplementation alternative to lysine-restricted diet.

19. Eur J Paediatr Neurol 2014; 18(6): 741-6. DOI: 10.1016/j.ejpn.2014.07.001. 17. Wu G, Morris Jr SM. Arginine Metabolism: Nitric Oxide and Beyond. Biochem J 1998; 336 (Pt 1) (Pt 1): 1-17. DOI: 10.1042/bj3360001.

20. Flynn NE, Meininger CJ, Haynes TE, Wu G. Themetabolic basis of arginine nutrition and pharmacotherapy.Biomed Pharmacother 2002; 56990:427-38. DOI: https://doi.org/10.1016/S0753-3322(02)00273-1.

21. Bahremand A, Ziai P, Khodadad TK, Payandemehr B, Rahimian R, Ghasemi A, et al. Agmatine enhances the anticonvulsant effect of lithium chloride on pentylenetetrazole-induced seizures in mice: Involvement of L-arginine/nitric oxide pathway. Epilepsy Behav 2010; 18(3): 186-92. DOI: 10.1016/j.yebeh.2010.04.014.

22. Yuzyuk T, Thomas A, Viau K, Liu A, De Biase I, Botto LD. Effect of dietary lysine restriction and arginine supplementation in two patients with

pyridoxine-dependent epilepsy. Mol Genet Metab 2016; 118(3): 167-72. DOI: 10.1016/j.ymgme.2016.04.015.

23. Paul V. The effect of N-nitro-L-arginine methyl ester posttreatment on the anticonvulsant effect of phenobarbitone and diazepam on picrotoxin-induced convulsions in rats. Pharmacol Biochem Behav 2003; 74(4): 789-94. DOI: https://doi.org/10.1016/S0091-3057(03)00028-5.

24. Sinha S, Siddiqui KA. Definition of intractable epilepsy. Neurosciences (Riyadh). 2011; 16(1):3-9.

25. Latorre G.[a] · Besa P.[a] · Parodi C.G.[b] · Ferrer V.[b] · Azocar L.[c] · Quirola M.[b] · Villarroel L.[d] · Miquel J.F.[c] · Agosin E.[e] · Chianale J.[c] Prevalence of Lactose Intolerance in Chile: A Double-Blind Placebo Study. Digestion 2014, Vol.90, No. 1

26. Saadi A, Patenaude B, Mateen FJ. Quality of life in epilepsy -31 inventory (QOLIE-31) scores: A global comparison. Epilepsy Behav 2016; 65:13-17. DOI: 10.1016/j.yebeh.2016.09.032.

27. Barbul A. Arginine: biochemistry, physiology, and therapeutic implications. JPEN J Parenter Enteral Nutr 1986; 10(2): 227-38. DOI: 10.1177/0148607186010002227.

28. de Boer J, Meurs H, Coers W, Koopal M, Bottone AE, Visser AC, Timens W, Zaagsma J. Deficiency of nitric oxide in allergen-induced.airwayhyperreactivity to contractile agonists after the early asthmatic reaction: an *ex vivo* study. *Br J Pharmacol* 1996; 119(6): 1109–16. DOI: 10.1111/j.1476-5381.1996.tb16011.x.

29. Ricciardolo FL, Di Maria GU, Mistretta A, Sapienza MA, Geppetti P. Impairment of bronchoprotection by nitric oxide in severe asthma. *Lancet* 1997; 350(9087): 1297–8. DOI: 10.1016/s0140-6736(05)62474-9.

30. Moncada S, Higgs A. The l-arginine-nitric oxide pathway. *N Engl J Med* 1993; 329(27): 2002–12.DOI: 10.1056/NEJM199312303292706

31. Rose WC, Haines WJ, Warner DT. The amino acid requirements of man. V. The role of lysine, arginine, and tryptophan. J Biol Chem 1954; 206(1): 421-30.

32. Mertz ET, Beeson WM, Jackson HD. Classification of essential amino acids for the weanling pig. Arch Biochem Biophys 1952; 38: 121-8. DOI: 10.1016/0003-9861(52)90015-5.

33. Heird WC, Nicholson JF, Driscoll Jr JM, Schullinger JN, Winters RW. Hyperammonemia resulting from intravenous alimentation using a mixture of synthetic L-amino acids: a preliminary report. J Pediatr 1972; 81(1): 162-5. DOI: 10.1016/s0022-3476(72)80396-2.

34. G.Wu and S. M. Morris Jr., "Arginine metabolism: nitric oxide and beyond," *Biochemical Journal*, vol. 336, no. 1, pp. 1–17, 1998.

35. Morris Jr SM. Arginine synthesis, metabolism, and transport: regulators of nitric oxide synthesis. In: Laskin JD, Laskin DL, editors. Cellular and Molecular Biology of Nitric Oxide. New York, NY, USA: Marcel Dekker; 1999. P. 57-85.

36. Wiesinger H. Arginine metabolism and the synthesis of nitric oxide in the nervous system. Prog Neurobiol 2001; 64(4):365-91. DOI: https://doi.org/10.1016/S0301-0082(00)00056-3.

37. Bagetta G, Iannone M, Scorsa A M, Nisticò G. Tacrine-induced seizures and brain damage in LiCl-treated rats can be prevented by Nω-nitro-L-arginine methyl ester. Eur J Pharmacol 1992; 213(2): 301-4. DOI: 10.1016/0014-2999(92)90695-z.

38. Coughlin CR, van Karnebeek CD, Al-Hertanic W, Shuen AY, Jaggumantri S, Jack RM, et al. Triple

therapy with pyridoxine, arginine supplementation and dietary lysine restriction in pyridoxine-dependent epilepsy: Neurodevelopmental outcome. Mol Genet Metab 2015; 116(1-2): 35-43. DOI: 10.1016/j.ymgme.2015.05.011.

39. Beamer E, Otahal J, Sills GJ, Thippeswamy T. N w-Propyl-l-arginine (L-NPA) reduces status epilepticus and early epileptogenic events in a mouse model of epilepsy: behavioral, EEG and immunohistochemical analyses. Eur J Neurosci 2012; 36(9): 3194-203. DOI: 10.1111/j.1460-9568.2012.08234.x.

40. Roksana B Zak [1], Clayton L Camic, Ethan C Hill, Molly M Monaghan, Attila J Kovacs, Glenn A Wright. Acute Effects of an Arginine-Based Supplement on Neuromuscular, Ventilatory, and Metabolic Fatigue Thresholds During Cycle Ergometry. Appl Physiol Nutr Metab 2015; 40(4):379-85.

41. Clayton L Camic [1], Terry J Housh, Jorge M Zuniga, Russell C Hendrix, Michelle Mielke, Glen O Johnson, Richard J Schmidt. Effects of Arginine-Based Supplements on the Physical Working Capacity at the Fatigue Threshold. J Strength Cond Res 2010; 24(5):1306-12.