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L-carnitine+piracetam for fatigue and muscular strength of patients with post-poliomyelitis

Abstract

Objective: Verify if L-carnitine associated with Piracetam in fixed dose combination improves fatigue and muscular strength (MS) in Post-Poliomyelitis Syndrome (PPS) patients and verify the tolerability and safety of the combination.

Methods: a randomized clinical study, double-blind, placebo-controlled was conducted, comparing the use of three tablets of the fixed dose combination (L-Carnitine 330mg, Piracetam 270 mg) twice a day, to your placebo.94 patients were evaluated over 180 days, where three evaluations (3 visits) took place; MS was assessed through the Medical Research Council Manual Muscular Test (MMT), the fatigue through the Fatigue Severity Scale (FSS) and Piper's Revised Fatigue Scale (PRFS).

Results: Only the group that received the active medication presented significant improvement in fatigue, both in the PRFS (V1: 5.73, V3: 4.36, $p = 0.001$) and FSS (V1: 53.1, V3: 49, 4, $p = 0.002$). A statistically significant improvement was observed in the proximal musculature of the lower limbs of the activr group (AG) (V1 78.99%; V 3 81.10%, $p = 0.040$). As in the MS of the proximal muscles of the right lower limb AG (V1 77.86% V3 81.69%, $p = 0.008$), the group that received the placebo (V1 79.67% V3 78.83%, $p = 0.035$). The placebo group (PG) had the highest MS decrease.Possible AE related to AG when compared to PG highlighted the high presence of headache and dry mouth that occurred more frequently in the PG. The other events reported didn't presented significant differences between the groups.

Conclusion: The combination of the drugs has shown to be effective for improving fatigue and MS in PPS patients, as well as delaying the progression of muscle weakness. The trial monitoring demonstrated safety and tolerability for this combination.

Keywords: fatigue, l-carnitine, muscle strength, post- poliomyelitis syndrome

Volume 5 Issue 6 - 2020

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Received: October 10, 2020 | **Published:** November 02, 2020

Introduction

Fatigue and new muscle weakness are among the most frequent and debilitating late symptoms of poliomyelitis, which cause great impairment in the functional capacity of patients with Post-Poliomyelitis Syndrome (PPS).[1–3]

New muscle weakness is typically asymmetrical and may occur in muscles previously affected by poliomyelitis, as well as in uninvolved muscles.[1,4] It can be permanent or transient. It usually progresses slowly, but sometimes develops in a subacute manner or progresses incrementally. Transient weakness is probably a manifestation of muscular fatigue.[5]

Fatigue occurs in about 60–89% of individuals with PPS.[5,6] The aetiology of the symptom arouses great interest, mainly due to its multi factorial character, and can be divided into two components: peripheral (muscular) fatigue and central (general) or simultaneously-occurring fatigue.[7]

As these are caused by the overuse of surviving motor neurons over the years, it leads to the disintegration of the terminal axons and an intense metabolic demand.[2,5]

Considering the importance of both symptoms and the limitations they can cause in PPS patients; this study aims to evaluate the effectiveness of the fixed dose combination of Piracetam with L-carnitine regarding fatigue and MS in this population.

Both drugs have their effects proven individually and are already used in clinical practice. Carnitine is a cellular component with a key rolein the mitochondrial oxidation of fatty acids; its supplementation suggests a greater fatty acid concentration, leading to availability of more energy for mechanical work, making it possible to delay the use of muscular glycogen, thus, delaying the development of fatigue.[8] Piracetam is a nootropic drug thatmplays a role in the cerebral metabolism, by increasing the energy efficiency of neurons, helping with the restoration of cortical cell function; thus, activating cognitive functions such as attention and memory, which are complaints seen in central fatigue, reported by the patients with PPS. Besides these effects the drugs have protective action on mitochondrial dysfunction. Recent researches evaluating the action of the fixed dose combination of L-carnitine with Piracetam have shown that when associated, they present synergic and complementary action protecting mitochondrial dysfunction.[9–12]

Objective

Verify if L-carnitine associated with Piracetam in fixed dose combination can improve fatigue and MS in patients with Post-Poliomyelitis Syndrome (PPS) and verify the tolerability and safety of the combination.

Materials and methods

Design and sample size

This was a double-blind randomised controlled clinical trial with 2:1 factorial design for the experimental group. The study was performed at the PPS outpatient clinic of the Department of Neuromuscular Diseases, Federal University of São Paulo (UNIFESP) in the years of 2017 and 2018.

For both outcomes, the sample size was calculated as the difference between means (test t) using the G*Power 3.1 software (Heinrich-Heine-University) using the following parameters: tails: two; error α: 0.05; power (1-error β): 0.80; allocation ratios: 1:1 and 2:1; correction for losses: 10%. In the Manual Muscular Test, a standard deviation of 6.9 was considered when performing the tests (13). The calculation was performed to detect a difference between the means of both the groups equal to or greater than 4 (Effect on size d: 0.5797101). Allocation ratio: 1:1, 2:1; non-central parameter δ: 2.8399879, 2.8399879; t critical: 1.9855234, 1.9825973; degrees of freedom: 94, 106; real power: 0.8025874, 0.8035051; sample size of group 1: 48, 72; sample size of group 1 corrected for losses (10%): 53, 80; sample size of group 2: 48, 36; sample size of group 2 corrected for losses (10%); total sample size: 96, 108; total sample size corrected for losses (10%).

For fatigue, a standard deviation of 1.7 was considered when performing the score ([14]). The calculation was performed to detect a difference between the means of the groups equal to or greater than 1 (Effect on size d: 0.5882353). Allocation ratio 1:1, 2:1; non-central parameter δ: 2.8515764, 2.48481401; degrees of freedom: 92, 104; real power: 0.8055819, 0.8055973, sample size of group 1: 47, 71; sample size of group 1 corrected to (10%): 52, 78; sample size of group 2: 47, 35; sample size of group 2 corrected for losses (10%): 52, 39; total sample size: 94, 106; total sample size corrected for losses (10%): 104, 117.

Considering the sample sizes calculated for both efficacy tests, the estimated number of subjects was 120 individuals.

Inclusion and exclusion criteria

Ambulatory subjects with PPS were included if they had: confirmed history of poliomyelitis; confirmed diagnosis of PPS;new muscle weakness for at least one year;aged between 22 and 60 years;examination of previous electroneuromyography andability to swallow the medication.

The exclusion criteria were: intolerance to L-carnitine or piracetan;use of L-carnitine or piracetan in the past three months; inability to understand the informed consent form (ICF) and to meet the study's requirements; anemia; glycated hemoglobin>7.0%; electrolyte Imbalance (Hypokalemia); kidney failure;urinary infection;thyroid dysfunction;cardiomyopathy; uncontrolled systemic arterial hypertension;autoimmune process;pregnancy;major depressive disorder;diabetes (Insulin needed);discontinuation of medication or placebo for more than 7 days.

Sampling and random assignment

The research population included 118 patients of the Department of Neuromuscular Diseases. Randomisation of treatment allocation was done in blocks of unequal sizes, that each one was a multiple of three, to respect the 2: 1 ratio between the groups.They were manually randomised by shuffling envelopes, based on blinding in a randomised clinical trial.

All treatment allocations were concealed for the patients as well as the researchers. The data analyst remained blinded until after the primary outcome analyses.

The placebo and the test medication were produced with the same organoleptic characteristics and had identical packages, which were individually identified by a sequential numerical code, following the principles of Good Practices Manufacturing.

Intervention and study stages

The patients were evaluated over 180 days, where three evaluations (3 visits) took place. Pharmacological treatment prior to the study was maintained according to medical advice.

Pre-Selection (Visit 0 - up to 60 days before visit 1)

The screening was held at an open meeting for clarification. A pre-selection was carried out with approximately 10 patients being called per week. All those who were selected signed the ICF. The selected patients were subject to blood sample collection (complete blood count, glycated hemoglobin, potassium, creatinine, TSH, free T4, βHCG), urine (urine 1) and electrocardiogram (ECG).

Initial assessment (Visit 1 -V1)

The clinical evaluation and analysis of the exams requested in the screening were done to check for possible AE. Evaluating the patient's fatigue and MS was also done.

Subsequent examinations were as follows: complete blood count, VHS, serum iron, ferritin, CRP, fasting glycemia, TSH, free T4, urea, creatinine, creatine phosphokinase, TGA, TGP, γGT, triglycerides, total cholesterol and fractions, protein electrophoresis, creatine kinase and urine type I.

After the evaluations, the dispensation was carried out of the active drugs (each tablet contains L-Carnitine 330mg + Piracetam 270 mg) for the experimental group and the placebo for the control group. It was advised to take, via oral route, three capsules twice a day.

All patients were instructed not to change their lifestyle during the study period. They were also asked to bring the packages to assess their adherenceto the treatment.

Intermediate evaluation (Visit 2 (V2) - D60±15 days)

60 days after starting the treatment, the evaluations carried out at V1 were repeated; as well as blood and urine laboratory exams, along with dispensing and counting of the medication, and checking for AE.

Final evaluation (Visit 3 (V3) - D180±15 days)

120 days after V2, the evaluations performed on V1 and V2 were repeated, counting the medication, checking for AE and performing laboratory tests.

Instruments

Fatigue severity scale (FSS)

described by Krupp et al. in 1989, addresses everyday situations correlated with the social aspects of the individual relating to the last two weeks. The instrument consists of nine statements where patients respond with numbers from 1 (disagree completely) to 7 (agree completely).[15] This instrument is one of the most used to assess the fatigue of PPS patients but only evaluates the peripheral fatigue and asconsequence the need to use another instrument that also covers the central fatigue.

Revised piper fatigue scale (RPFS)

has a high internal awareness (Cronbach alfa = 0.97), a study with a population of patients with PPS found good psychrometric properties including high simultaneous validity. The instrument is composed of 22 alternative and 5 descriptive questions that address the sensory, cognitive, mood, behavioural, severity and affective

aspects of fatigue. The patient should score each item from 0–10. The descriptive questions are not part of the score; they serve to provide qualitative data.[16]

Medical research council manual muscular test (MMT)

in general, the clinical examination of MS in patients with neuromuscular diseases is carried out using this scale. The Medical Research Council Manual Muscular Test– MMT was developed in 1943, originally for MS assessment in patients with poliomyelitis sequel. The test consists of scores ranging from 0–5 points for each tested muscle group,[17] 0 indicating that there is no muscle contraction and 5 corresponding to normal muscular strength.

The tested muscle groups were: flexors and extensors of the cervical spine, upper body, shoulder, elbow, wrist, fingers, knee, ankle, toes; abductors and adductors of shoulder and hip.

After the MS assessment, the percentage of strength was computed using the Medical Research Council (MRC) index.

MRCindex:

$$\frac{\text{score sum x 100}}{\text{number of tested muscles x 5}}$$

The muscles were grouped in different ways to assess distal and proximal components of MS in these patients.

Statistical analysis

Data was processed using a microcomputer, in the database of Excel Office 2010. A statistical analysis was obtained with the help of SPSS V20, Minitab 16 and Excel Office 2010. The following tests were used:

i. ANOVA Test to compare the qualitative variable's averages.

ii. ANOVA Test with Repeated Measures to compare the qualitative variable'saverages.

iii. Two-Proportion Parity Test was used to compare the distribution of the relative frequency (percentages) of the qualitative variables between groups.

iv. Tukey's Multiple Comparison (Post Hoc) was used to compare study visits.

Confidence Interval (CI) for the mean to analyse how much the average may vary with a certain confidence probability. All CIs were created with a 95% statistical confidence. A significance level of 0.05 (5%) was established.

Results

Of 118 initial patients, 24 discontinued treatment (Figure 1: 15 from the AG, and 9 from the PG). The reasons among others were: abandonment (AG: 60%, PG: 88.9%), recurrent adverse event (AG: 20%, PG: 0%), alterations in biochemical tests (AG: 0%), frequent alcohol consumption (AG: 6.7%, PG: 11.1%), Amyotrophic Lateral Sclerosis (AG: 6.7%, PG: 0%). There was no statistically significant difference between groups.

The study's non-adherence was 2.46% ± 1.97% in the PG, and 2.63% ± 3.63% in the AG (p = 0.808).

The sample's characteristics are shown in Table 1. The values for the total fatigue score are shown in Table 2, as well as the PRFS's dimensions. When comparing fatigue between visits in the total score, only the AG showed a statistically significant difference FSS: V1-V2 p = 0.001, V1-V3 p = 0.012; PRFS: V1-V2 p = 0.001, V1-V3 p = <0.001.

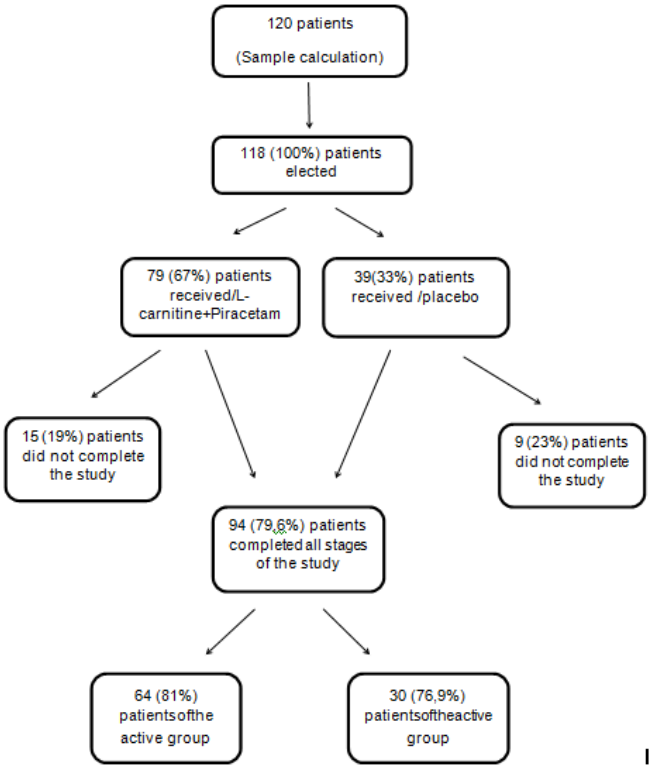

Figure 1 Trial patient flowchart.

Statistically significant differences were found in the behavioural dimension in V1 compared to the other visits (V1-V2 p = 0.003; V1-V3 p = 0.001). The same was also observed in the other dimensions, affective: V1 with V2 p = 0.001 V1 with V3 p = 0.001; psychological: V1-V2 p = 0.002; V1-V3 p = 0.001.

Table 3 shows the classificationof fatigue's according to the instruments as well as its variation, also with a comparison between study visits.

Due to the patient'sMS data extension, only the statistically significant values were shown, available in Table 4.

Safety and tolerability

Possible AE related to the AG when compared to PG highlighted the high presence of headache and dry mouth along with gastrointestinal disorders such as intestinal constipation, epigastric pain, nausea and seasickness, dizziness, insomnia, tachycardia and sleepiness.

The distribution of headache and dry mouth events occurred more frequently in the PG, with significant differences in incidence between the two groups in the trial; headache AG = 18 (60,0%) PG= 22 (34,4%) p= 0,019 and dry mouth AG = 6 (20,0%) PG= 3 (4,7%)p= 0,019.Other reported AE did not present statistically significant values between the groups.

The AE reported are of mild intensity, common frequency, not serious and with possible or probable causality with L-Carnitine and Piracetam; therefore, the study demonstrated safety and tolerability of this association in relation to the monitoring of AE without presenting clinically significant alterations; and perceived predictable events

as described in companies' inserts of L-carnitine or Piracetam. The fixed combination presented safety in relation to the monitoring of laboratory parameters since it did not present clinically relevant changes.

Table 1 Characteristics of the sample

	Ative Group		Placebo Group		P-value
	N	average (sd)	N	average(sd)	
Age	64	48,8±6,3	30	48,4±7,1	0,789
Age of acute polio	64	2,1±2,21	30	1,3±0,70	0,055
Age of SPP	64	39,6±9	30	37,7±8,4	0,345
Stability plate	64	39±8,4	30	38,8±7,5	0,903
Age group of the Poliomyelitis	N	%	N	%	
< 1 month	2	3,10%	0	0,00%	0,328
1 month to 11 months	20	31,30%	9	30,00%	0,903
1 year to 1 year 11 months	20	31,30%	13	43,30%	0,253
2 years to 2 years and 11 months	8	12,50%	7	23,30%	0,181
3 years to 3 years and 11 months	2	3,10%	1	3,30%	0,957
4 years to 4 years and 11 months	3	4,70%	0	0%	0,228
> 5 years	9	14,10%	0	0%	0,031
Years of study					
From 0 to 7 years	10	15,60%	4	13,30%	0,771
From 8 to 10 years	6	9,40%	1	3,30%	0,298
From 11 to 14 years	27	42,20%	15	50,00%	0,478
15 or more years	21	32,80%	10	33,30%	0,96
Gender					
Female	37	57,80%	24	80,00%	0,036
Male	27	42,20%	6	20,00%	

Two-proportion parity test; ANOVA Test

Table 2 FSS and PRFStotal score

		Average(SD)		CV		Min- Max		CI		P-value	
		AG	PG	AG	PG	AG	PG	AG	PG	AG	PG
FSS	V1	53,1 ± 9,3	51,4 ± 10,8	17%	21%	14 - 63	21 - 63	2,3	3,9	0,002	0,554
	V2	48,7 ± 11,7	48,3 ± 12,7	24%	26%	Oct-63	16 - 63	2,9	4,6		
	V3	49,4 ± 10,3	48,3 ± 10,6	21%	22%	22 - 63	15 - 61	2,5	3,8		
PRFS	V1	5,73 ± 2,76	4,69 ± 3,15	48%	67%	0 - 10	0 - 8,78	0,68	1,13	0,001	0,79
	V2	4,28 ± 3,28	4,62 ± 3,07	77%	66%	0 - 9,75	0 - 8,55	0,8	1,1		
	V3	4,36 ± 3,07	4,34 ± 3,19	70%	74%	0 - 9,28	0 - 9,03	0,75	1,14		
Behavioural Dimension	V1	5,98 ± 2,82	4,85 ± 3,36	47%	69%	0 - 10	0 - 9,33	0,69	1,2	0,003	0,72
	V2	4,51 ± 3,49	4,94 ± 3,37	77%	68%	0 - 9,83	0 - 9,5	0,85	1,21		
	V3	4,54 ± 3,23	4,5 ± 3,41	71%	76%	0 - 9,83	0 - 9,5	0,79	1,22		
Affective Dimension	V1	5,75 ± 2,96	4,83 ± 3,38	52%	70%	0 - 10	0 - 10	0,73	1,21	0,001	0,809
	V2	4,2 ± 3,42	4,66 ± 3,21	81%	69%	0 - 10	0 - 0,98	0,84	1,15		
	V3	4,29 ± 3,34	4,45 ± 3,31	78%	74%	0 - 9,8	0 - 0,92	0,82	1,18		
Psychological	V1	5,56 ± 2,81	4,51 ± 3,02	51%	67%	0 - 10	0 - 9,64	0,69	1,08	0,002	0,812
Dimension	V2	4,18 ± 3,23	4,4 ± 2,98	77%	68%	0 - 10	0 - 8,36	0,79	1,07		
	V3	4,27 ± 3,00	4,18 ± 3,14	70%	75%	0 - 9,64	0 - 8,91	0,73	1,12		

ANOVA Test with Repeated Measures; Tukey's Multiple Comparison (Post Hoc). FSS, Fatigue Severity Scale; PRFS, Piper Revised Fatigue Scale; SD, standard derivation; Min, minimum values; Max, maximum values; CV, coefficient of variability; CI, Confidence Interval.

Citation: Motta MP, Quadros AAJ, Quadros MSB, et al. L-carnitine+piracetam for fatigue and muscular strength of patients with post-poliomyelitis. *Int Phys Med Rehab J.* 2020;5(6):220–228. DOI: 10.15406/ipmrj.2020.05.00261

Table 3 Classification of the fatigue according to the instruments

Classification of the fatigue		Visit 1		Visit 2		Visit 3		P-value between visits		
		N	%	N	%	N	%	V1-V2	V2-V3	V1-V3
FSS										
Active Group	Absent	1	1,60%	2	3,10%	3	4,70%	0,559	0,648	0,31
	Light	3	4,70%	9	14,10%	6	9,40%	0,069	0,41	0,3
	Moderate	18	28,10%	23	35,90%	25	39,10%	0,344	0,715	0,19
	Severe	42	65,60%	30	46,90%	30	46,90%	0,033	1	0,033
Placebo Group	Absent	2	6,70%	3	10,00%	3	10,00%	0,64	1	0,64
	Light	1	3,30%	3	10,00%	0	0,00%	0,301	0,076	0,313
	Moderate	7	23,30%	9	30,00%	13	43,30%	0,559	0,284	0,1
	Severe	20	66,70%	15	50,00%	14	46,70%	0,19	0,796	0,118
PRFS										
Active Group	Absent	7	10,90%	19	29,70%	17	26,60%	0,008	0,694	0,024
	Light	5	7,80%	6	9,40%	8	12,50%	0,752	0,571	0,38
	Moderate	17	26,60%	18	28,10%	16	25,00%	0,843	0,689	0,84
	Intense	35	54,70%	21	32,80%	23	35,90%	0,013	0,71	0,033
Placebo Group	Absent	8	26,70%	8	26,70%	9	30,00%	1	0,774	0,774
	Light	2	6,70%	1	3,30%	1	3,30%	0,554	1	0,554
	Moderate	6	20,00%	6	20,00%	6	20,00%	1	1	1
	Intense	14	46,70%	15	50,00%	14	46,70%	0,796	0,796	1

Two-Proportion Parity Test; Tukey's Multiple Comparison (Post Hoc).

Table 4 MMT and MRC Index

Decreased muscle strength				Average - sd	CV	Min - Max	CI	P-value	P-value between visits		
									V1-V2	V2-V3	V1-V3
Cervical	Flexion	PG	V1	4,87 ± 0,35	7%	4 – 5	0,12	0,044	0,161	0,043	0,423
			V2	4,93 ± 0,25	5%	4 – 5	0,09				
			V3	4,8 ± 041	8%	4 – 5	0,15				
Trunk	Flexion	PG	V1	4,77 ± 0,5	11%	3 – 5	0,18	0,044	1,000	0,012	0,031
			V2	4,77 ± 0,5	11%	3 – 5	0,18				
			V3	4,57 ± 0,68	15%	3 – 5	0,24				
Wrist and left hand	5° finger Abduction	AG	V1	4,88 ± 0,49	10%	2 – 5	0,12	0,046	0,159	0,228	0,019
			V2	4,81 ± 0,61	13%	2 – 5	0,15				
			V3	4,73 ± 0,65	14%	2 – 5	0,16				
Right Hip	Flexion	PG	V1	3,73 ± 1,23	33%	1 – 5	0,44	0,007	0,326	0,003	0,017
			V2	3,77 ± 1,25	33%	1 – 5	0,45				
			V3	3,5 ± 1,41	40%	1 – 5	0,5				
Left hip	Flexion	AG	V1	3,81 ± 1,42	37%	0 – 5	0,35	0,035	0,05	0,06	0,727
			V2	3,92 ± 1,42	36%	0 – 5	0,35				
			V3	3,78 ± 1,37	36%	0 – 5	0,34				
Improvement of muscle strength				**Average - sd**	**CV**	**Min - Max**	**CI**	**P-value**	**P-valor between visits**		
									V1-V2	**V2-V3**	**V1-V3**
Right Shoulder	Flexion	AG	V1	4,48 ± 1,07	24%	0 - 5	0,26	0,024	0,196	0,006	0,132
			V2	4,38 ± 1,21	28%	0 - 5	0,3				
			V3	4,61 ± 0,92	20%	0 - 5	0,23				

Citation: Motta MP, Quadros AAJ, Quadros MSB, et al. L-carnitine+piracetam for fatigue and muscular strength of patients with post-poliomyelitis. *Int Phys Med Rehab J.* 2020;5(6):220–228. DOI: 10.15406/ipmrj.2020.05.00261

Table continue

Improvement of muscle strength				Average - sd	CV	Min - Max	CI	P-value	P-valor between visits		
									V1-V2	V2-V3	V1-V3
Wrist and right hand	Opponent of the thumb	AG	V1	4,45 ± 0,71	16%	2-5	0,17	<0,001	0,863	0,003	<0,001
			V2	4,44 ± 092	21%	0 - 5	0,23				
			V3	4,73 ± 0,67	14%	02-5	0,16				
Wrist and left hand	opponent of the right thumb	AG	V1	4,28 ± 1,000	23%	0 -5	0,24	<0,001	1,000	<0,001	<0,001
			V2	4,28 ± 9,97	23%	0 - 5	0,24				
			V3	4,64 ± 0,72	16%	02-05	0,18				
		PG	V1	4,27 ± 0,78	18%	02-05	0,28	0,001	0,161	0,005	<0,001
			V2	4,4 ± 0,72	16%	02-5	0,26				
			V3	4,7 ± 0,65	14%	02-5	0,23				
Right Hip	Abduction	AG	V1	3,92 ± 1,34	34%	0 - 5	0,33	0,001	0,001	0,541	0,002
			V2	4,19 ± 1,23	29%	0 - 5	0,3				
			V3	4,25 ± 1,2	28%	0 - 5	0,29				
		PG	V1	4,07 ± 1,16	29%	01-5	0,42	0,019	0,009	0,415	0,174
			V2	4,43 ± 0,86	19%	02-5	0,31				
			V3	4,33 ± 1,03	24%	01-5	0,37				
Right ankle	Dorsiflexão	AG	V1	3,28 ± 1,87	57%	0 - 5	0,46	0,038	0,419	0,011	0,025
			V2	3,25 ± 1,86	57%	0 - 5	0,46				
			V3	3,53 ± 1,75	49%	0 - 5	0,43				
	Eversion	AG	V1	3,47 ± 1,99	57%	0 - 5	0,49	0,045	0,109	0,021	0,124
			V2	3,38 ± 1,96	58%	0 - 5	0,48				
			V3	3,64 ± 1,78	49%	0 - 5	0,44				

MRCIndex

Proximal muscles			Média - dp	CV	Min - Max	CI	P-value	P-value between visits		
								V1-V2	V2-V3	V1-V3
Lower member	AG	V1	78,99 ± 18,92	24%	12,5 - 100	4,64	0,04	0,022	0,715	0,041
		V2	80,75 ± 17,49	22%	15 - 100	4,29				
		V3	81,1 ± 17,04	21%	15 - 100	4,18				
Right lower limb	AG	V1	77,86 ±24,27	31%	5 - 100	5,95	0,008	0,014	0,216	0,005
		V2	80,13 ± 22,96	29%	5 - 100	5,63				
		V3	81,69 ± 23,23	28%	5 - 100	5,69				
	PG	V1	79,67 ± 19,87	25%	35 - 100	7,11	0,035	0,039	0,042	0,691
		V2	82,67 ± 17,89	22%	40 - 100	6,4				
		V3	78,83 ± 20,95	27%	20 - 100	7,5				

ANOVA Test with Repeated Measures; Tukey's Multiple Comparison (Post Hoc). SD, standard derivation Min: minimum values; Max, maximum values; CV, coefficient of variability; CI, Confidence Interval

Discussion

To this day, the treatment of fatigue and MS in PPS is based on a non-pharmacological approach, lifestyle changes, physiotherapy, training programs and the prevention of secondary complications. Pharmacological options are not currently available yet.

Both Piracetam and L-carnitine play roles in energy metabolism, L-carnitine's action is more evident at muscle level, whereas Piracetam's action is at the brain. As such, this research can evaluate the two origins of fatigue referred to by PPS patients, as well as changes in these patients' MS. No parallel was found in the literature, attesting to the ground-breaking aspect of this research. Two other studies evaluated the drugs together, but they useddistinct populations and differed from the objective and methodology of this research. However, the studies have shown the drugs have good bioavailability in conjunction and act in concentrations below the needed ones to act individually.[10,18] Costa RAP et al.[10] further found that the drugs act on mitochondrial metabolism, preventing and/or improving mitochondrial dysfunction.

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Other studies provided by Biolab Pharmaceuticals assessed the action of L-carnitine associated with Piracetam. Paim BA et al.[9] found a protective effect of the drugs against simvastatin-induced mitochondrial swelling in mitochondria isolated cells from heart, liver and musculoskeletal. Gagliano & De Nucci[11] have shown that the combination of the fixed dose L-carnitine with Piracetam positively interferes in the mitochondrial metabolism, protecting muscle cells from myopathy induced by simvastatin.In addition, Ilha & De Nucci,[12] showed that the active principles did not present pharmacokinetic interaction, thus maintaining the individual effects of each drug. Silva FS. in your master dissertation compared Piracetam + L-carnitine to three other protective solutions and reported that the combination produced activation of Akt ($p \leq 0.05$). Akt, is a serine/threonine-specific protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcriptionand cell migration. It is involved in cellular survival pathways by inhibiting apoptotic processes as well ascapable of inducing protein synthesis, thus being a key signaling protein in cell pathways leading to skeletal muscle hypertrophy and general tissue growth.[19]

L-carnitine has an intrinsic interaction with bioenergetics processes, such as the transportation of fatty acids to the cellular mitochondria, transforming them in energy; it participates in the control of the mitochondrial acyl-CoA/CoA ratio, and in the perixisomal oxidation of fatty acids and production of ketone bodies. Thus, playing an important role in diseases linked to metabolic impairment.[20]

Skeletal muscles are the main reservoir of L-carnitine, its concentration is at least 50 to 200 times higher than in blood plasma. The daily requirement of L-carnitine is supplied to the body through endogenous biosynthesis and exogenous sources. Thus, carnitine's homeostasis is maintained by a moderate rate of internal carnitine synthesis, dietary intake and efficient management by the kidney.[21]

It is suggested that patients with PPS present lower levels of carnitine in their skeletal muscles due to residual atrophy and new progressive muscular atrophy, which will contribute further to this deficiency, increasing the muscular metabolic deficit, and explaining the fatigue so prevalent in this population.

A study of Amyotrophic Lateral Sclerosis concluded that carnitine deficiency may influence the progression of systemic muscular atrophy.[22]

It showed that the muscles preferentially affected by the poliomyelitis virus[23–25] were the ones where the most MS improvement was observed. This is probably because they have lower concentrations of carnitine and a higher energy deficit. With L-carnitine supplementation, these muscles will benefit from higher amounts of ATP through the oxidation of fatty acids, enhancing muscular performance.[8] Therefore, this explains the MS improvement.

In addition, patients with PPS have a higher number of type I muscle fibres;[26] L-carnitine shows a predilection for this type of fibre, leading to its hypertrophy. This is because L-carnitine acts on the oxidative metabolism, characteristic of this muscle fibre. It also participates in the removal of lactic acid from blood and muscles.[27] Seeing as how these patients perform their daily activities in the same proportion as high intensity physical exercise,[28] this promotes a reduction of free carnitine leading to lactate and pyruvate accumulation, which causes muscle fatigue.[29,8]

Thompson RT et al.[30] assessed changes in high energy phosphates and intramuscular pH during physical exercise in patients with PPS, finding no metabolic abnormalities. However, these did not differentiate between the after-effects severity of the studied patients. Jagannathana NR & Wadhwab S[31] assessed the residual after-effects of acute poliomyelitis with magnetic resonance imaging, finding a relationship between the presence or absence of intramyocellular lipids and the paralysis severity. Patients with severe after-effects showed absence of intramyocellular lipids, as well as a shortage or absence of creatinine, carnitine, and choline.

Two hypotheses were suggested for Piracetam's role in improving musculoskeletal symptoms; the first one was as follows: Piracetam provides an increase in fluidity of the mitochondrial membrane,[32] acting as a regulator of mitochondrial function, due to the increased mobility and function of respiratory complexes;[33] and the second one was: Piracetam promotes an improvement in the synaptic function,[34] thus, playing an indirect role on the muscles of patients with PPS. Therefore, it provides a decrease in fatigue and increased MS in patients with PPS.

The PG has shown a greater decrease in MS than the AG, suggesting that the fixed dose combination of L-carnitine with Piracetam and besides improving energy metabolism also slowed the progression of muscle weakness.In accordance with the actual knowledge, the role of Akt activation in the muscular strength and mass increase makes possible to speculate that this result could be explained by the action of the fixed combination activating the Akt signalling chain.

A carnitine deficiency is known to have significant deleterious effects on the Central Nervous System.[20] The poliomyelitis virus also damaged some brain regions;[35] as the brain is one of the areas responsible for the synthesis of carnitine,[8] it is suggested that these lesions may further interfere with the metabolism of carnitine, which is already deficient in individuals with PPS. Thus, it can be said that fatty acids are not metabolised as they should be, increasing the concentration of saturated fatty acids in the membranes of brain cells, leading to symptoms related to central fatigue. L-carnitine is responsible for the removal of acyl-CoA compounds such as carnitine esters from mitochondria, resulting in a reduced ion flow in the respiratory chain, thus, avoiding the decrease of mitochondrial membrane fluidity.[36]

Piracetam will potentiate this action, since it acts as a 'metabolic booster' modulating brain functions, acting with the mitochondrial membrane to increase its fluidity,[32,33] therefore improving complaints related to central fatigue.

The treatment of fatigue and MS of patients with PPS using the fixed dose combination of L-carnitine with Piracetam was shown to be effective, with symptom improvement being proven. This is due to a good bioavailability of drugs, and their synergist actions.

Conclusion

The study population reflects the sample present at the PPS outpatient ward in the Sector of Research of Neuromuscular Diseases of UNIFESP, with an average age of 48,7 years, with the female sex being the most prevalent one.

The patients in this study had both peripheral fatigue, and central fatigue. The fixed dose combination of L-carnitine with Piracetam allowed to ascertain:decreased fatigue in all its aspects; increased MS in some muscle groups;areduced sample of muscle groups with decreased strength; demonstrated safety and tolerability in relation to the monitoring of AEs and laboratorial parameters.

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Acknowledgements

The authors thank the research participants; and Biolab Sanus Farmacêutica Ltda. who donated all the medications used, as well as the placebo, the company owns the patent for the medication used (PCT/BR2009/000053).

Conflicts of interest

Marcio Falci Doctor, was in the period of the study the advisor to the Scientific Presidency of Biolab Sanus Farmacêutica Ltda. And he is the inventor of the product. With no participation of data collection and analysis. The other authors don't report any conflict of interest.

References

1. Dalakas MC. The post-polio syndrome as an evolved clinical entity: Definition and clinical description. *Ann N Y Acad Sci*. 1995;753:68–80.
2. Oliveira ASB, Maynard FM. Post-poliomyelitis syndrome: Neurological aspects. *Rev Neurociências*. 2002;10(1):31–34.
3. Conde MTRP, Oliveira AS, Quadros AAJ, et al. Post-polio syndrome: Epidemiologic and prognostic aspects in Brazil. *Acta Neurol Scand*. 2009;120:191–197.
4. Quadros AAJ, Conde MTRP, Marin LF, et al. Frequency and clinical manifestations of post-poliomyelitis syndrome in a Brazilian tertiary care center. *Arq Neuropsiquiatr*. 2012;70(8):571–573.
5. Trojan DA. A Case–control study of risk factors for postpoliomyelitis syndrome. [master's thesis]. montreal: department of epidemiology and biostatistics, McGill University; 1992.
6. Trojan DA, Cashman NR, Shapiro S, et al. Predictive factors for post-poliomyelitis syndrome. *Arch Phys Med Rehabil. Jul*. 1994;75(7):770–777.
7. Ostlund G, Ake W, Sunnerhagen KS, et al. Post-polio syndrome: fatigued patients a specific subgroup?. *Journal of Rehabilitation Medicine.* 2011;43(1):35–41.
8. Bras EP. Supplemental carnitine and exercise. *Am J Clin Nutr*. 2000;7:618S–23S.
9. Paim BA, Carvalheiro RA, Vercesi AE. Atividades protetoras dos compostos l-carnitina e piracetam, frente ao inchamento mitocondrial induzido por estatinas bem como por outros compostos indutores do processo de inchamento mitocondrial. Laboratorio de Bioenergética da Universidade Estadual de Campinas,São Paulo, Brazil. Relatório Final Projeto Piracar Convenio 4198 Período de 01/02/2009 a 31/01/2010.
10. Costa RAP, Fernandes MP, De Souza-Pinto NC, et al. Protective effects of l-carnitine and piracetam against mitochondrial permeability transition and PC3 cell necrosis induced by simvastatin. *European Journal of Pharmacology*. 2013;701(1–3):82–86.
11. Gagliano T, De Nucci G. Estudo de Biodisponibilidade Comparativa de uma Formulação de piracar (3 comprimidos contendo cada um 270mg de Piracetam e 330mg de L-carnitina; Biolab Sanus Farmacêutica Ltda.) versus uma Formulação de nootropil (1 comprimido contendo 800 mg de Piracetam; Sanofi Aventis Farmacêutica Ltda.) em voluntários sadios de ambos os sexos. Campinas: Galeno Desenvolvimento de Pesquisas Ltda., 2014:27 .
12. Ilha JO, De Nucci G. Estudo clínico bifásico, unicêntrico, randomizado, controlado por placebo, de grupos paralelos, para avaliação da eficácia, tolerabilidade e segurança da combinação em dose fixa de Levocarnitina e piracetam na miopatia induzida pelo uso crônico de sinvastatina. Campinas: Galeno Desenvolvimento de Pesquisas Ltda, 2015:50.
13. On AY, Oncu J, Atamaz F, et al. Impact of post-polio-related fatigue on quality of life. *J Rehabil Med*. 2006;38(5):329–332.
14. Rekand T, Gramstad A, Vedeler CA. Fatigue, pain and muscle weakness are frequent after Guillain-Barré syndrome and poliomyelitis. J Neurol Mar. 2009;256(3):349–354.
15. Mendes MF, Pavan K, Marangoni BE, et al. Cross-cultural of the fatigue severity scale to Portuguese language. *Med reabil*. 2008;27(3):69–71.
16. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: A practical guide for clinicians and researchers. *Journal of Psychosomatic Research*. 2004;56:157–170.
17. Florence JM, Pandya S, King WM, et al. Intrarater reliability of manual muscle test (Medical Research Council scale) grades in Duchenne's muscular dystrophy. *Physical Therapy*. 1992;72(2):115–122.
18. Mendes GD, Zaffalon GT, Silveira AS, et al. Assessment of pharmacokinetic interaction between piracetam and l-carnitine in healthy subjects. *Biomed Chromatogr*. 2016;30(4):536–542.
19. Lima FS. Métodos de cardioproteção em modelo de isquemia e reperfusão aguda em porcinos [Master's thesis].Campinas: Universidade Estadual de Campinas, Faculdade de Ciencias Médicas;2015.
20. Virmani A, Binienda Z. Role of carnitine esters in brain neuropathology. *Molecular Aspects of Medicine*. 2004;25:533–549.
21. Ramsay RR, Gandour RD, van der Leij FR. Molecular enzymology of carnitine transfer and transport. *Biochim. Biophys Acta*. 2001;1546:21–43.
22. Isse N, Miura Y, Obata T, et al. Carnitine deficiency presenting with a decreased mental state in a patient with amyotrophic lateral sclerosis receiving long-term tube feeding: A case report. *J Med Case Rep*. 2013;7:286.
23. Kumar K, Kapatia NK. The pattern of muscle involvement in poliomyelitis of the upper limb. *International Orthopaedics (SICOT).* 1986;10:11–15.
24. Sharma SC, Sangwam SS, Siwach RC, et al. The pattern of residual muscle paralysis in poliomyelitis. *International Orthopaedics (SICOT).* 1994;18:122–125.
25. Lal SK, Ram KV. Behaviour of untreated affected muscles of the lower limbs in polio. *Indian J Pedlar*. 1970;37:572.
26. Borg K, Borg J, Dhoot GK, et al. Motoneurone firing and isomyosin type of muscle fibres in prior polio. *J Neurol Neurosurg Psychiatry*. 1989;52:1141–1148.

27. Pekala J, Patkowska-Sokola B, Bodkowski R, et al. L-Carnitine - metabolic functions and meaning in humans Life. *Curr Drug Metab*. 2011;12(7):667–78.
28. Thomas CK, Zijdewind I. Fatigue of muscles weakened by death of motoneurons. *Muscle Nerve*. 2006;33(1):21–41.
29. Sahlin K. Muscle carnitine metabolism during incremental dynamic exercise in humans. *Acta Physiol Scand*. 1990;138:259–262.
30. Thompson RT, Barton, PM, Marsh GD, et al. Post-polio fatigue: A 31P magnetic resonance spectroscopy investigation. *Orthopedics*. 1991;14(11):1263–1267.
31. Jagannathan NR, Wadhwa S. In vivo proton magnetic resonance spectroscopy (MRS) study of post-polio residual paralysis (PPRP) patients. *Magnetic Ressonance Imaginig*. 2002;20(1):113–117.
32. Muller WE, Koch S, Scheuer K, et al. Effects of pira- cetam on membrane fluidity in the aged mouse, rat, and human brain. *Biochern Pharmacol*. 1997;53:135–140.
33. Ricchellii F, Gobbo S, Moreno G, et al. Changes of the fluidity of mitochondrial membranes induced by the permeability transition. *Biochemistry*. 1999;38(29):9295–9300.
34. Winblad B. Piracetam: A review of pharmacological properties and clinical uses. *CNS Drug Reviews*. 2005;11:169–182.
35. Bodian D. Histopathologic basis of clinical findings in poliomyelitis. *Am J Med*. 1949;6:563–578.
36. Kumaran S, Savitha S, Anusuya Devi M, et al. L-carnitine & DL-α-lipoic acid reverse the age-related deficit in glutathione redox state in skeletal muscle and heart tissues. *Mechanisms of Ageing and Development*. 2004;125(7):507–512.

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