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Assessment of a fixed-dose combination of l-carnitine + piracetam in the treatment of pain in post-poliomyelitis syndrome

Abstract

Introduction: Pain is one of the most frequent symptoms of Post Poliomyelitis Syndrome (PPS) and its treatment also includes medication. The no otropic agent Piracetam enhances neuronal effectiveness and the compound L-Carnitine generates muscle energy. Considering that pain in PPS is related to muscle overuse or disuse, it is assumed that supplementation with a fixed-dose combination of L-Carnitine + Piracetam improves muscle performance, reducing pain.

Objective: To analyze the effect of a fixed-dose combination of L-Carnitine + Piracetam on pain in PPS patients.

Method: A randomized, double-blind clinical trial, has compared the use of a fixed-dose combination of L-Carnitine + Piracetam to placebo, in the treatment of pain in 94 patients at the PPSambulatory care center of *UNIFESP*.

Results: Both groups reported a reduction inpain, however, only the active group improved functional performance after using the medication.

Conclusion: the use of a fixed-dose combination of L-Carnitine + Piracetam is efficient in the treatment of pain in PPS patients.

Keywords: drug treatment, L-carnitine, pain, piracetam, post poliomyelitis syndrome, rehabilitation

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Introduction

Post-Polio Syndrome (PPS) is a disorder of the nervous system that can break out in individuals who have suffered from polio.[1–4] Symptoms include reacquired muscle weakness, fatigue, and muscle and joint pain, which may result in impaired functionality.[5]

Pain is one of the most frequent occurrences in PPS, being reported by up to 86% of patients.[6] Its origin is predominantly related to impaired body mechanics, caused by either musculoskeletal overuse or disuse.[6] To help diagnosis, PPS was divided into three categories: type I pain is post-polio pain, which occurs only in the muscles affected by it; type II pain includes injuries to tissues, muscles, tendons, bursae and ligaments; type III pain, or biomechanical pain, occurs due to joint degeneration.[7]

Energy preservation is of paramount importance in the treatment of PPS and Guidelines for Rehabilitation of People with PPS syndrome and co-morbidities advocate managing pain through physical rehabilitation, lifestyle changes and drug treatment.[8]

Physical rehabilitation helps in the improvement of body mechanics, in gait adjustments, and in muscle and joint overload relief.[7,8] Lifestyle changes include daily routine changes, home and workplace adaptations, weight control and compliance with pain-relief domestic guidelines, such as limbering, heat applications, self-massage and rest.[7–8] Drug treatment is essential for pain control in PPS and, to date, benzodiazepine-class muscle relaxants are the most efficient drugs.[7,11]

Several drugs have been evaluated in the treatment of PPS pain, including prednisone, amantadine, and intravenous immunoglobulin, but none of them have shown entirely satisfactory results.[12–14]

Piracetam is a nootropic agent, distinguished by increasing neuron efficiency, restoring the functioning of cortical cells and activating cognitive functions[15] and L-Carnitine is a quaternary ammonium compound, which facilitates the intramitochondrial transportation of fat in type 1 muscle fiber, generating energy for the functioning of muscles.[16,17]

Considering that pain in PPS is associated with musculoskeletal activity (overuse or disuse), it is assumed that supplementation with a fixed-dose combination of L-Carnitine + Piracetam improves energy performance of muscles and, hence, reduces pain.

Objectives

To analyze the therapeutic effect of a fixed-dose combination of L-Carnitine + Piracetam in the pain of patients with PPS.

Method

This was a randomized, double-blind, placebo-controlled clinical trial that compared the use of a fixed-dose combination of L-Carnitine + Piracetam to placebo, as an adjuvant therapy in the treatment of pain in patients with PPS. It was approved by the *Comitê de Ética e Pesquisa – CET* (Ethics and Research Committee) of the *Universidade Federal de São Paulo-UNIFESP/EPM* (Federal University of São

Paulo), under no. 1228/2015 and is part of the phase III, randomized, double-blind, placebo-controlled study to assess the therapeutic effect of a combination of L-Carnitine + Piracetam as an adjuvant therapy in the treatment of weakness, fatigue, and pain in patients with PPS (CEP n° 1808/11). The medication that has been used was donated by *Biolab Sanus Farmacêutica Ltda.* (patent no. PCT/BR2009/ 000053).

94 patients from the Post-Poliomyelitis Syndrome ambulatory care center of the Neuromuscular Diseases Research Unit at the *Universidade Federal de São Paulo – UNIFESP* (Federal University of São Paulo) took part in the study. Participants were randomized (2:1) for oral treatment with a fixed-dose combination of L-Carnitine (300 grams) + Piracetam (270 grams), 2 pills, 3 times a day; or placebo, with similar coloring, taste and identical packaging.

After signing the Informed Consent Form, were included in the study patients with confirmed diagnosis of PPS (diagnostic criteria used in accordance with the established by the European Federation of Neurological Societies-EFNS and the March of Dimes Birth Defects Foundation); muscle and/or joint pain; age between 22 and 60; and who had been undergoing ambulatorial treatment at least one month prior to the randomization. L-Carnitine-intolerant patients were excluded, as well as patients who had been using it for the prior three months; vegetarians; and patients with associated diseases.

Information on the patients' clinical condition was collected in a specific form, where data were collected on mobility (residual sequelae, use of orthoses and walking aids, associated musculoskeletal diseases), pain aspects (period and location), domestic actions for pain relief (heat application, self-massage, rest, limbering, medication) and physiotherapeutic treatment (hydrotherapy, kinesiotherapy, acupuncture, massage). The Visual Analog Scale for Pain (VAS Pain) was used to assess the participants' pain intensity and the Multidimensional Pain Inventory (MPI) measured the impact of pain on the participants' lives. The MPI consists of 52 questions, divided into 3 sectors: The 1st sector (1S) assesses pain intensity and interference in the patient's lifestyle; the 2nd sector (2S) refers to the reaction and behavior of third parties regarding the individual's pain; and the 3rd sector (3S) measures the interference of pain in the patient's daily activities. The score is calculated by the total of points in each sector, with the scores for the 1st and 2nd sectors being directly proportional to the interviewee's pain and the score for the 3rd sector being inversely proportional to the interviewee's pain.

The statistical treatment was done with: ANOVA Test; Student's T-Test; Correlation Test; Two-Proportion Equality Test; and P-Value.

Participants were divided into two groups – Active Group (AG) and Placebo Group (PG) – and submitted to clinical evaluation before (Visit 1 - V1 = D1), during (Visit 2 - V2 = D60 ± 15 days) and after using the medication (Visit 3 - V3 = D180 ± 15 days). The scales were applied on the first and last visits and the dispensing of medication on the first and second visits.

Results

The study showed a predominance of females (AG = 57.8%/PG = 80%); the average age of AG was 48.8 (median 49; ± 6.4) and of PG 48.5 (median 49; ±7.0). The analysis of clinical characteristics shows monoparesis as the predominant sequel due to polio (52.2%), followed by diparesis, with 38.3%. Limb shrinkage and/or scoliosis were present in 79.8% of the participants. The use of orthoses and walking aids was related by 58.5%, and out of the 41.5% who declared performing independent walking, 19.2% did not abide the prescription of auxiliary devices. Regarding pain manifestation, 69.1% of the participants declared having pain in the limb affected by polio, in the limb less affected by polio, and in the unaffected limb. Pain during and after physical activities was reported by 91.5% of patients.

The combination of types I, II and III of pain was present in 37.2% of the participants and type I pain (exclusively in the limb affected by polio) was present in 14.9% of the study population. Regarding pain intensity, the study population presented a higher intensity in the right hip joint (VAS-Pain 6.6) and lumbar region (VAS-Pain 6.2). Among musculoskeletal diseases, arthrosis was the most frequent, reported by 41.5% of participants, followed by tendinitis at 34%.

In the analysis of patients' adherence to home guidelines for pain management, the results have shown that 74.5% of the participants followed only one of the recommendations and none of them obeyed all the guidelines. 76.5% of participants did not submit themselves to physical therapy, of which 78.7% had received such a treatment prescription. Hydrotherapy and kinesiotherapy were the most frequent methods among the 23.5% of participants who underwent physical therapy.

In assessing the effects of the medication, the analysis of the Visual Analogue Scale (VAS) showed a reduction in the average intensity of pain in both groups after the use of the medication (AG: V1 = 5.0/V3 = 4.2 /p-value = 0.009; PG: V1 = 5.0/V3 = 3.8/p-value = 0.03).

An analysis of the MPI showed that both the AG and the PG exhibited a decrease in the scores of the 1st and 2nd sectors. In the 3rd Sector, the AG exhibited an increase in score while the PG exhibited a decrease.

Discussion

Pain is part of the human being's life and follows him throughout his existence. The personal and subjective character of pain makes research on its evaluation and treatment challenges to overcome.

At first glance, pain is a phenomenon related to tissue injury, however, its emotional and cognitive aspects are relevant and must be considered, given that, regardless of location, origin, extension or intensity, the painful experience causes an impact, and an impact that might be relevant to the point that it guides the individual's life.

As well as the studies carried out by Werhagem and Borg[18] & Hirsh et al.[19] this study had a larger percentage of females as its participants. The average age detected excludes elder participants, who suffer increasing pain due to the physiological aging process.[20] The predominance of monoparesis found in the present study opposes the results found by Quadros,[6] where diparesis (36.4%) and quadriparesis (29.5%) prevailed.

Discrepancies in the lower limb length and scoliosis are common in people with polio sequelae and are listed among the main diseases responsible for pain in the population with PPS.[6] Biomechanical impairment is directly linked to pain in PPS patients, specifically type III pain,[21] because it can contribute to the emergence or evolution of conditions such as arthrosis, arthritis, low back pain, herniated disc, tendinitis and bursitis.

In this study, limb shrinkage, scoliosis or both conditions were found in 79.8% of the population. These data may be related to some factors, such as the percentage of patients with arthrosis; greater intensity of pain in the hip joint and lumbar region; the report of pain during and after physical activities; and, finally, the manifestation

of pain both in the limb affected by polio and in the non-affected limb. In addition to the physical aspect, poor adherence to physical therapy treatment and non-compliance with domestic guidelines may contribute to increased pain in patients with PPS.

The analysis of the medication effects shows a statistically significant decrease in the average pain intensity on the VAS-Pain scale in both groups, however, the difference between the groups did not show significance (p-value = 0.52).

The results of the MPI analysis show that the AG presented a statistically significant decrease in the 1st sector, indicating a decrease in the intensity of pain and its interference in their daily lives, after the use of the medication. Although the PG has also shown a decrease in the score, such decrease was not statistically significant. The results of the AG in the 3rd Sector of the MPI showed a significant increase in the score, indicating that after the use of medication, the participants' ability to perform daily activities had increased. On the other hand, the score of the 3rd Sector for the PG decreased significantly, what demonstrates greater difficulty in carrying out daily tasks.

Costa et al.[22] showed that the combination of a fixed-dose combination of L-Carnitine and Piracetam interferes positively with mitochondrial metabolism, protecting cells from oxidative damage; therefore, the decrease in the intensity of pain and the increase of the physical capability of the AG may be related to the enhancement of the patients' muscular condition, provided by the medication; in other words, the improvement of muscular condition resulted in a decrease in pain and such improvement allowed the accomplishment of a greater number of activities.[22]

The AG results are coherent when comparing MPI and VAS-Pain, as they show a reduction in pain intensity and interference, confirmed by the increase in the capability to perform daily activities. The same does not happen with the PG, which, despite having reported a reduction in pain intensity and interference in VAS-Pain and MPI, has not shown an increase in the capability to perform daily activities, that is, has not shown clinical improvement.

The explanation for the results reported by the PG participants might be related to the placebo effect. In an experiment carried out by Ader et al., eight out of ten patients with multiple sclerosis showed a reduction in the level of white blood cells (leukocytes) after administration of a placebo drug.[23] The observational response in the placebo effect, that happens when the observation of a positive reaction in someone else is enough to generate the same response,[24] may also be related to the results of the present study, since the participants of both groups were evaluated on the same date.

Another element to be taken into account when analyzing the placebo group's results is the emotional element. The relationship between pain and psychological suffering has been verified in several studies with PPS patients[10] and it has been proven that the emotional element can be as significant as the sensitive one[25] regarding pain.

It is possible, therefore, that the PG results were influenced by the aspects aforementioned, which would justify a report of improved pain perception that cannot be proven by clinical improvement.

Conclusion

The analysis indicates that the use of a fixed-dose combination of L-Carnitine + Piracetam as an adjuvant in the treatment of pain, in patients with SPP, is efficient when taken into account the enhancement of functionality in the AG. However, the AG has shown subtle improvement when compared to the PG, rendering essential new studies to demonstrate the effectiveness of the medication.

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Conflicts of interest

Dr. Marcio Falciis the Advisor to the Scientific Chair of Biolab Sanus Farmaceutica Ltda is the Clinical Research Manager of BiolabSanus Farmacêutica Ltda, howewever, as they did not participate in any stage of the study, any bias in the research results were prevented. The other participants of the research presented no conflicts of interests.

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