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A randomized controlled trial of coenzyme Q_{10} for fatigue in the late-onset sequelae of poliomyelitis

Margaret M. Peel [a], Marie Cooke [a,*], Helen J. Lewis-Peel [a], Rodney A. Lea [b], Wendy Moyle [a]

[a] NHMRC Centre for Research Excellence in Nursing Interventions, Menzies Health Institute Queensland, Centre for Health Practice Innovation, Griffith University, Queensland, Australia
[b] Institute of Health and Biomedical Innovation, Queensland University of Technology, Queensland, Australia

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ABSTRACT

Objective: To determine if coenzyme Q_{10} alleviates fatigue in the late-onset sequelae of poliomyelitis.
Design: Parallel-group, randomized, placebo-controlled trial.
Background setting: Coenzyme Q_{10} has been shown to boost muscle energy metabolism in post-polio subjects but it does not promote muscle strength, endurance or function in polio survivors with post-poliomyelitis syndrome. However, the collective increased energy metabolism might contribute to a reduction in post-polio fatigue.
Participants: Polio survivors from the Australian post-polio networks in Queensland and New South Wales who attribute a moderate to high level of fatigue to their diagnosed late-onset sequelae of poliomyelitis. Those with fatigue-associated comorbidities of diabetes, anaemia, hypothyroidism and fibromyalgia were excluded.
Method: Participants were assigned (1:1), with stratification of those who use energy-saving mobility aids, to receive 100 mg coenzyme Q_{10} or matching placebo daily for 60 days. Participants and investigators were blinded to group allocation. Fatigue was assessed by the Multidimensional Assessment of Fatigue as the primary outcome and the Fatigue Severity Scale as secondary outcome.
Results: Of 103 participants, 54 were assigned to receive coenzyme Q_{10} and 49 to receive the placebo. The difference in the mean score reductions between the two groups was not statistically significant for either fatigue measure. Oral supplementation with coenzyme Q_{10} was safe and well-tolerated.
Conclusion: A daily dose of 100 mg coenzyme Q_{10} for 60 days does not alleviate the fatigue of the late-onset sequelae of poliomyelitis.
The registration number for the clinical trial is ACTRN 12612000552886.

1. Introduction

Along with new and increasing muscle weakness and fatigability, joint and muscle pain, excessive and unaccustomed general fatigue is a major symptom of the late-onset sequelae of poliomyelitis (LOSP), including post-poliomyelitis syndrome (PPS). Cold intolerance, pulmonary dysfunction, sleep disorders, speech and swallowing difficulties, and muscle atrophy, twitching and cramping are other symptoms that may occur.[1] These symptoms typically develop after several decades of stable physical functioning following the initial recovery phase from acute poliomyelitis infection. Of these, fatigue has been reported as the major disabling symptom and a persistent problem in polio survivors with LOSP.[2,3] The fatigue is multidimensional comprising general, physical, and mental fatigue.[4] However, vitality (or the absence of general fatigue) in PPS depends on physiological rather than psychological parameters.[5] Although the fatigue does not affect cognitive functioning[6] or significantly impair mental health,[7] it does negatively impact physical and psychosocial functioning in polio survivors with LOSP.[7]

Coenzyme Q_{10} (CoQ_{10}), or ubiquinone, is an essential cofactor in oxidative phosphorylation which takes place in the mitochondria of cells with the production of ATP that provides energy for metabolic processes. A pilot study, published in 1997, showed that a daily dose of 100 mg CoQ_{10} boosted the skeletal muscle energy metabolism in subjects with PPS, as measured by nuclear magnetic resonance, to a significantly greater extent than it did in age-matched, healthy controls after 3 months and progressively by 6 months.[8] A follow-up

* Corresponding author.
E-mail address: m.cooke@griffith.edu.au (M. Cooke).

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pilot study, published in 2008, showed that CoQ_{10} supplementation during a resistance training program conferred no additional benefit on muscle strength, endurance or function in PPS subjects as compared to the resistance training program alone in control PPS subjects.[9] Because of the enhanced muscle energy metabolism, we initiated a parallel-group, randomized, double-blind, placebo-controlled trial to determine whether daily oral supplementation by 100 mg of CoQ_{10} for 60 days can alleviate the fatigue of LOSP.

2. Method

2.1. Design and participants

Trial participants were recruited from the Queensland and New South Wales post-polio networks. The post-polio networks are support groups for polio survivors with LOSP that has been diagnosed by practitioners in neurology or rehabilitation medicine with recognized expertise in this specialty. Eligible participants are those who attribute a moderate to high level of fatigue primarily to LOSP and who are not already taking CoQ_{10}. Exclusion criteria are a diagnosis of diabetes, anaemia, hypothyroidism, and fibromyalgia which are other major medical causes of fatigue. In addition, treatment with warfarin (Coumadin® or Marevan®) or dabigatran (Pradaxa®) is contraindicated for CoQ_{10} supplementation because of potential interactions.[10,11]

In the first phase of recruitment, two members of the research team made presentations to the Queensland post-polio networks, with the exception of one network in Far North Queensland. The presentations covered the principles of randomized controlled trials, the purpose of the proposed trial and the need for participants to experience a moderate to high level of fatigue that they attribute to LOSP. The first mail-out included a research project information sheet and the consent form. In addition to conforming to the eligibility criteria, participants were asked to sign an agreement to give a blood sample for the determination of CoQ_{10} plasma concentrations within 24 h of taking the last capsule, later changed to within 6 h of taking any one of the last five capsules. Participants were also asked to make no significant change to their diet or exercise program that might affect their energy levels for the duration of the trial.

On receipt of the signed consent form, each participant was contacted by phone to check their eligibility. A form for the collection of demographic and clinical characteristics was posted to those whose eligibility was confirmed. The form included a question on whether power wheelchairs or mobility scooters were used as the sole or major means of mobility. The energy cost of walking in ambulatory polio survivors with lower limb paralysis, with or without walking aids, is significantly higher, by an average of about 40%, than that for age- and sex-matched, healthy subjects.[12] This energy demand would contribute to fatigue. Two self-administered questionnaires were included for the assessment of fatigue at baseline. These were the multidimensional assessment of fatigue, MAF[13] and the fatigue severity scale, FSS.[14]

2.2. Randomization and masking

An independent, automated web-based service at the Griffith University Clinical Trials Coordination Centre (CTCC) randomly assigned participants to receive CoQ_{10} or placebo capsules on a 1:1 basis according to a computer-generated sequence for block sizes of four or six, with stratified assignment of those who use energy-saving power wheelchairs or mobility scooters as their sole or major means of mobility. World Health Limited, who donated the CoQ_{10} capsules and provided the placebo capsules, labelled the capsule containers with identical labels for the CoQ_{10} and placebo groups except for an individual number which was different on each label ('3000'–'3110'). These container numbers aligned to the randomisation matrix sequence provided by CTCC for either the CoQ_{10} or placebo capsules. As participants were enrolled and randomized, we assigned the allocated container numbers to them. A novel colloidal formulation with enhanced enteral absorption and bioavailability was used as delivery system for the CoQ_{10}.[15] The placebo was a non-soy, non-nut, vegetable oil in matching soft gel capsules. Participants and investigators were blinded to group allocation for the duration of the study.

2.3. Procedures

After phone contact with each participant, we posted the capsules in insulated packages by express post for delivery on the next business day. This procedure minimized exposure of the capsules to high ambient temperatures since CoQ_{10} should be maintained below 30°Celsius. Each participant was contacted again by telephone to confirm receipt and to ask their starting date for taking the capsules. The packages included a diary for recording daily intake of a capsule, with breakfast, and a business-size card that warned against continuing to take the capsules should treatment with warfarin or dabigatran be instituted.

About 10 days before the end of the 60-day period of taking capsules, we posted each participant a Request Form for the collection of a blood sample at a pathology collection centre for the determination of plasma CoQ_{10} concentrations. All samples were submitted for analysis to a Department of Chemical Pathology at a Queensland tertiary hospital. This mail-out also included the final fatigue questionnaires and a questionnaire that actively surveyed the responses that participants may have experienced to oral ingestion of the capsules.

2.4. Assessment of fatigue

The primary outcome was fatigue reduction as assessed by the MAF (© Basia Belza 1993; e-mail contact for permission to use is PROinformation@mapi-trust.org). The MAF is a multidimensional measure that addresses degree and severity, distress caused, interference with the activities of daily living, as well as the daily pattern and timing of the fatigue.[13] The secondary outcome was fatigue reduction as assessed by the FSS, a unidimensional measure that focuses on the impact of fatigue on the activities of daily living.[14] Our choice of these fatigue measures was based on the recommendations of Whitehead[16] who reported that the MAF and FSS instruments were among only six of 22 fatigue measures that had robust psychometric properties and among only four that demonstrated the ability to detect changes in fatigue over time or after intervention. The MAF is a 16-item questionnaire that yields a global fatigue index (GFI) ranging from 1 (no fatigue) to 50 (severe fatigue).[13] Most of the questions (numbers 4–14) are directed to the degree to which fatigue interferes with the activities of daily living. The MAF has not been used previously for the measurement of fatigue in PPS but it is a revision of the multidimensional Piper Fatigue Scale, which has been validated as a reliable measure of fatigue in post-polio patients.[17] The MAF has also been validated for the assessment of multidimensional fatigue in a wide range of other populations and was reported as the only multidimensional measure that is capable of detecting change, provided that change is not small.[16] The FSS comprises nine items in a seven-point scale with higher scores in the range of 1–7 indicating higher levels of fatigue.[14] Vasconcelos et al.[18] compared the applicability and validity of the FSS, visual analog scale and the fatigue impact scale for the measurement of fatigue in PPS and concluded that the FSS was the strongest predictor of severe fatigue and most closely agreed with the intensity of self-reported fatigue in PPS. Since then, Rasch