The Efficacy and Safety of Coenzyme Q10 in Preventing the Progression of Early Parkinson's Disease: A Meta-Analysis

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ABSTRACT

Introduction. Coenzyme Q10, also known as Ubiquinone, is a substance now being used as a dietary supplement in many countries including the Philippines. It has also been the focus of several researches as treatment for several diseases including Parkinson's Disease. Several studies have shown that Coenzyme Q10 inhibits mitochondrial dysfunction in Parkinson's Disease, hence delaying its progression.

Objectives. The objective of this study is to assess and summarize the available evidence on the efficacy and safety of Coenzyme Q10 administration in the prevention of the progression of early Parkinson's Disease.

Methods. This is meta-analysis of randomized controlled trials on the use of Coenzyme Q10 in Parkinson's Disease. A literature search in several databases was conducted for relevant studies. Three randomized controlled trials met the inclusion criteria. The efficacy of Coenzyme Q10 were measured using the total and the component scores of the Unified Parkinson Disease Rating Scale on follow-up. On the other hand, safety were measured using the withdrawal rate and the associated adverse reactions during the therapy of CoQ10. The Review Manager Software was utilized for the meta-analysis.

Results. Compared to Placebo, treatment of CoQ10 did not show any significant difference in the mean scores of the UPDRS mental and ADL scores. Interestingly, the UPDRS motor score showed a significant difference between Coenzyme Q10 and placebo, but no significant difference when a subgroup analysis between high-dose (-4.03 [-15.07-7.01], p-value 0.47, I^2 67%, P for heterogeneity 0.08) and low-dose Coenzyme Q10 (0.53 [-0.89-1.94], p-value 0.47, I^2 34%, P for heterogeneity 0.22) was done. Overall, there was no significant difference in the total UPDRS score (0.68 [-0.61-1.97], p-value 0.30, I^2 0%, P for heterogeneity 0.70). The most common side effects of the use of Coenzyme Q10 are anxiety, back pain, headache, sore throat, nausea, dizziness and constipation.

Conclusion. Contrary to some animal and human studies, this meta-analysis showed that the use of CoQ10 results to non-significant improvement in all components of the UPDRS scores as opposed to placebo. However, the use of CoQ10 is tolerated and seems to be safe but further studies are needed to validate this finding.

Key Words: neuroprotection, Parkinson's disease, CoQ10

Introduction

Parkinson's Disease (PD) is one of the most common multicentric neurodegenerative disorder with its burden likely to double in 2030.[1] It has the classic symptoms of bradykinesia, muscular rigidity and resting tremors. These symptoms were found to occur when there is already 60% dopaminergic neuron loss and inclusion formation in the substantia nigra pars compacta.[2] Currently, dopamine replacement therapy with Levodopa is widely prescribed as the first-line treatment, however, it does not provide protection against the progression of PD.[3,4] Thus, neuroprotective strategies to delay the progression of this disease are now becoming important considerations in the overall treatment.[5] Four neuroprotective strategies seem to have promising effects in delaying the progression of PD: 1) enhanced mitochondrial function, 2) anti-inflammatory mechanisms, 3) calcium channel blockade and 4) uric acid elevation.[6]

Mitochondrial dysfunction, being one of the key mechanisms of the pathogenesis of PD, had been the focus of research in the past decades. Mitochondrial dysfunction causes oxidative stress, damage to mitochondrial DNA and altered mitochondrial morphology eventually leading to neuronal demise.[7] Coenzyme Q10 (CoQ10), an agent also known as 2,3-dimethoxy-5-methyl-6-decaprenyl benzoquinone or Ubiquinone, was found to inhibit mitochondrial dysfunction and apoptosis by alteration of the mitochondrial membrane permeability. It functions as an obligatory co-factor in Complex I/II and as a coenzyme in Complex III in the electron transport chain for the energy production of the cell.[2] It also prevents the formation of reactive oxygen species, hence its anti-oxidative effect.[8] Brains of patients with PD have shown both a decrease in antioxidant nutrients and enzymes within cells of the substantia nigra.[9] Several animal studies proved that

Poster presented at the 12th International Conference on Alzheimer's and Parkinson's Diseases, March 18-22, 2015, Nice, France and at the 56th Annual Meeting of the Japanese Society of Neurology, May 20-23, 2015, Niigata, Japan.

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administration of CoQ10 protects the substantia nigra from further damage. However, human studies showed conflicting results in the early and symptomatic stage of PD.[10] In a study by Shults et al., there was a delay in the progression of functional decline observed among early PD patients given 1,600 mg/day of CoQ10.[11] On the other hand, in a study done by Matthews et al., there was no significant change in the mitochondrial metabolism in patients using CoQ10.[12]

Objectives

The objective of this study is to assess, summarize and conduct a meta-analysis of the available evidence from randomized controlled trials (RCTs) for the efficacy and safety of Coenzyme Q10 administration in the prevention of the progression of early Parkinson's Disease.

Methods

Study Identification

All relevant published and unpublished RCTs comparing CoQ10 with placebo for prevention of the progression of early PD were identified. In this study, early PD is described as having only mild symptoms or corresponding to Hoehn and Yahr Stage ≤ 2.5. A literature search in several databases (MEDLINE, SCOPUS, ClinicalTrials.gov, ClinicalKey and Cochrane) from 1990-2014 was conducted for relevant abstracts using the terms Parkinson's Disease, Coenzyme Q10, neuroprotection, randomized controlled trial and controlled clinical trial. A review of bibliographies of retrieved studies was also done to locate additional unpublished studies. Full texts and additional information regarding the relevant studies were sought by correspondence with the authors through electronic mail.

Study Selection

Criteria for inclusion were 1) studies with subjects older than 25 years of age of either sex, diagnosed with early PD, 2) randomization done while subjects are not yet and never have been on symptomatic treatment at the entry to the study, 3) comparison of Coenzyme Q10 with placebo as a neuroprotective agent in PD and 4) use of objective measures or standardized scales to measure desired outcomes. Studies not fulfilling all the four criteria were excluded in the study.

Assessment of Study Quality

The quality of the included studies were assessed according to the Cochrane Collaboration Handbook Criteria version 5.1. These criteria include 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data and 6) selective reporting.

Data Extractions

Necessary information from the included studies were extracted using a standardized checklist to record the details on 1) method of randomization, 2) blinding and intention-to-treat analysis, 3) participant demographics, 4) comparison of outcomes, 5) withdrawal rate and 6) adverse events.

Outcomes

The efficacy of COQ10 in the prevention of the progression of PD were measured using the total and the component scores of the Unified Parkinson Disease Rating Scale (UPDRS) on follow-up of at least six months. The UPDRS is the most evaluated and valid rating scale for evaluation of PD. It evaluates several components consisting of activities of daily living, motor function and cognition.[13] On the other hand, safety were measured using the withdrawal rate and the associated adverse reactions during the therapy of CoQ10.

Statistical Analysis

Because of the likelihood of statistical heterogeneity, the random effects model was used. Tests for heterogeneity were also calculated. The Review Manager (RevMan) Software was utilized for all statistical analysis.[14]

Results

Study Selection

The process of study selection identified 478 potentially relevant articles (Figure 1). After thorough scanning of titles and abstracts, 470 articles were excluded and only eight studies were retained for further evaluation. The included studies were evaluated using the Jadad scale (Table 1). The Jadad scale is a valid and reliable tool to assess RCTs.[15] The process was done with two other colleagues to minimize bias. Four studies had a Jadad score of ≤ 3, hence were excluded

Table 1. Jadad Grading of Screened Studies for Meta-analysis

Studies	Randomization	Blinding	Withdrawal	Total
Parkinsons Study Group (2014)	1	2	1	4
Seet RC et al. (2014)	0	0	1	1
NINDS (2007)	2	2	1	5
Storch A et al. (2007)	2	2	1	5
Shults CW et al. (2004)	0	0	1	1
Muller T et al. (2003)	2	1	0	3
Shults CW et al. (2002)	2	2	1	5
Strijks E et al. (1997)	0	0	1	1

from the meta-analysis.[10,16-18] One of the studies, even with a Jadad score of 5 was still excluded from the meta-analysis because some patients were found to be on symptomatic treatment for their PD.[19] Aside from the Jadad score, the risks of bias were also assessed. Only the three randomized, placebo-controlled, double-blind studies, with a Jadad score of 4 or 5, were included in the meta-analysis.[20-22]

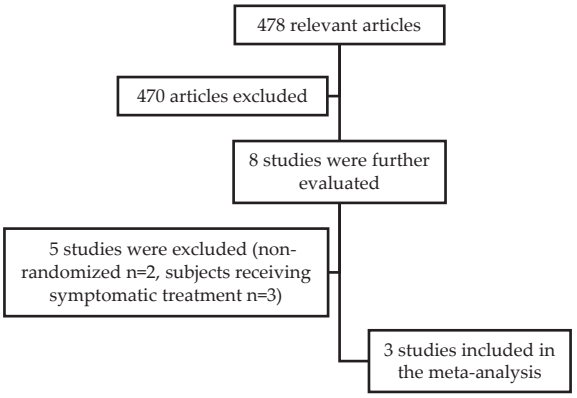

Figure 1. Process of Study Selection.

Study Quality

The quality of the three included RCTs were further evaluated using the criteria from the Cochrane Collaboration Handbook. Randomized sequence allocation were computer-generated in two of the included studies, however, in the second study, the method of randomization was not stated.[20-22] In the three included studies, concealment of the treatment allocation and blinding of the participants and observers were ensured. The use of UPDRS as an objective outcome measurement tool was also common in all the three studies. Also, the intention-to-treat principle was utilized in all of the studies. Since all of the included studies were assessed to have plausible risks unlikely to seriously affect the results of the study, then the three studies were deemed of low risk for bias.

Outcomes

A total of 822 subjects from the three RCTs were included in the study. The mean total and component UPDRS scores were computed and pooled from the available data in each study. The standard deviation was also extracted using the available p-value and standard errors.

The data on the outcomes generated from the RevMan software were shown (Figures 2 and 3). Compared to placebo, treatment of CoQ10 did not show any significant difference in the mean scores of the UPDRS mental (0.08 [-0.17–0.32], p-value 0.53, I^2=27%, P for heterogeneity 0.32), and ADL scores (0.27 [-0.91–1.46], p-value 0.65, I^2=71%, P for heterogeneity 0.03). Interestingly, the UPDRS motor score (3.01 [0.21–5.82], p-value 0.04, I^2=74%, P for heterogeneity 0.02) showed a significant difference between Coenzyme Q10 and placebo, though the studies included were found to be heterogenous in this aspect. Overall, there was no significant difference in the total UPDRS score (0.68 [-0.61 – 1.97], p-value 0.30, I^2=0%, P for heterogeneity 0.70).

Table 2. Adverse Drug Events, Placebo vs. Coenzyme Q10 (%)

	Placebo (N/290, %)	NINDS (N/71, %)	Shults et al. (N/64, %)	PSG (N/397, %)	Total (N/532, %)
Anxiety	24 (8)	9 (13)	--	25 (6)	34 (6)
Back pain	14 (5)	6 (8)	6 (9)	22 (6)	34 (6)
Headache	22 (8)	10 (14)	6 (9)	17 (4)	33 (6)
Sore throat	6 (2)	4 (6)	9 (14)	16 (4)	29 (5)
Nausea	23(8)	8 (11)	6 (9)	14 (4)	28 (5)
Dizziness	16 (5)	9 (13)	5 (8)	13 (3)	27 (5)
Constipation	16 (5)	6 (8)	--	20 (5)	26 (5)
Insomnia	11 (4)	6 (8)	--	19 (5)	25 (5)
Diarrhea	17 (6)	5 (7)	5 (8)	15 (4)	25 (5)
Tremor	12 (4)	1 (1)	--	23 (6)	24 (5)
Depression	20 (7)	8 (11)	--	15 (4)	23 (4)
Fall	13 (4)	4 (6)	4 (6)	12 (3)	20 (4)
Infection, bacterial	3 (0)	--	4 (6)	14 (4)	18 (3)
Cough	16 (6)	13 (18)	3 (5)	--	16 (3)
Sinusitis	9 (3)	5 (7)	9 (14)	--	14 (3)
Heartburn	5 (2)	9 (13)	5 (8)	--	14 (3)
Joint pain	13 (4)	7 (10)	5 (8)	--	13 (2)
Hypertension	0 (0)	--	--	12 (3)	12 (2)
Infection, viral	2 (0)	--	12 (19)	--	12 (2)
Edema	4 (1)	9 (13)	--	--	9 (2)
Fatigue	9 (3)	3 (4)	3 (5)	--	6 (1)
Flatulence	1 (0)	--	6 (9)	--	6 (1)
Myalgia	1 (0)	--	5 (8)	--	5 (0)
Influenza-like symptoms	2 (0)	4 (6)	--	--	4 (1)
Urinary frequency	1 (0)	3 (4)	--	--	3 (0)
Hypercholesterolemia	6 (2)	1 (1)	2 (3)	--	3 (0)
Bruise	5 (2)	2 (3)	--	--	2 (0)
Rash	4 (1)	2 (3)	--	--	2 (0)
Urinary urgency	1 (0)	2 (3)	--	--	2 (0)
Loss of appetite	3 (1)	1 (1)	--	--	1 (0)

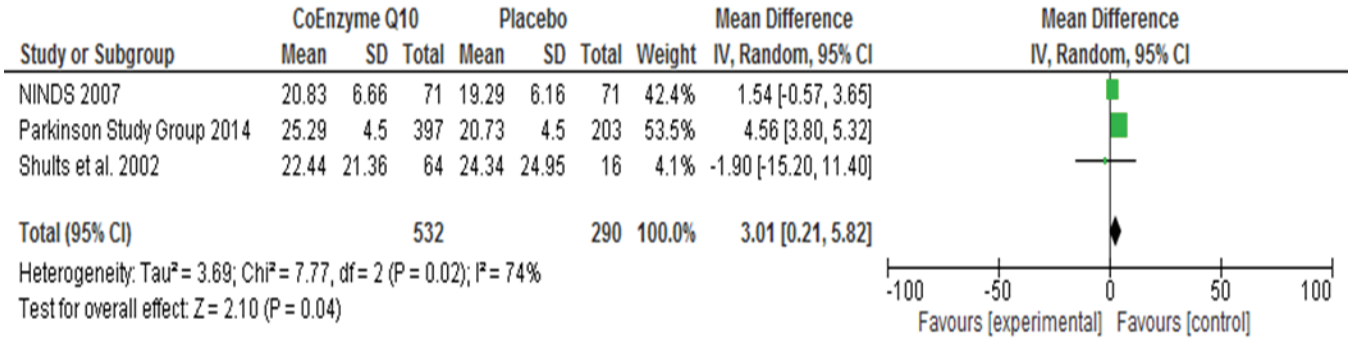

Figure 2. Mean Scores in Motor UPDRS score using Coenzyme Q10 versus Placebo for the Prevention of the Progression of Parkinson's Disease.

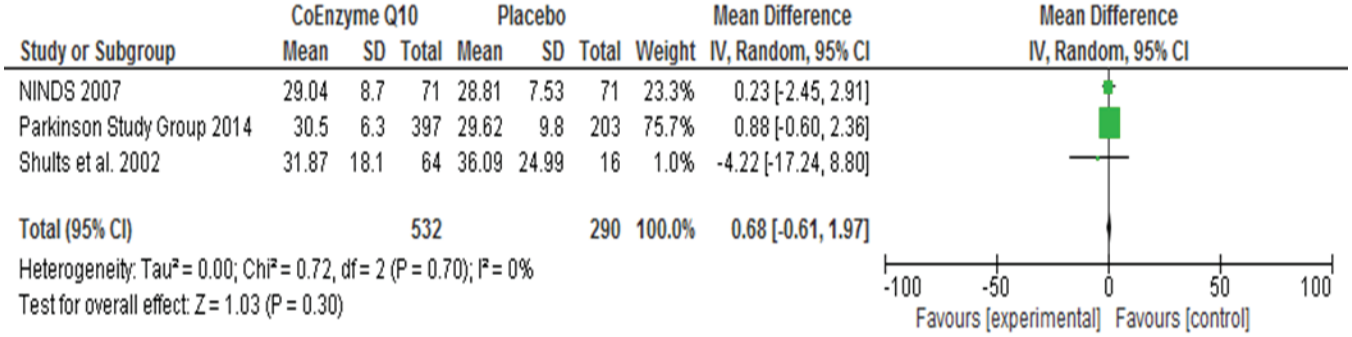

Figure 3. Mean Scores in the Total UPDRS score using Coenzyme Q10 versus Placebo for the Prevention of the Progression of Parkinson's Disease.

There is only a low and comparable withdrawal rate in the studies involved (14 subjects or 3% in the Coenzyme Q10 group versus 11 subjects or 4% in the placebo group). The given reasons for withdrawal in the treatment group were allergic reaction, heartburn and lack of desire to participate while in the placebo group were blood clot, nausea, prostatitis and change in urine color. Among those who completed the study, the most common side effects of the use of Coenzyme Q10 are anxiety, back pain, headache, sore throat, nausea, dizziness and constipation. Other noted events are insomnia, diarrhea, tremor, infection, fall, depression, cough, sinusitis, heartburn, joint pain, hypertension, edema, fatigue, flatulence, myalgia, urinary frequency, hypercholesterolemia, bruise, rash, urinary urgency and loss of appetite (Table 2).

Subgroup Analysis

A subgroup analysis between high-dose and low-dose Coenzyme Q10 versus placebo was done to determine if there is indeed a significant change in the UPDRS Motor score. High dose CoQ10 was arbitrarily set at greater than 1,200 mg while low-dose CoQ10 were those dosages below it. In this subgroup analysis, no significant difference was noted in the high-dose CoQ10 (-4.03 [-15.07–7.01], p-value 0.47, I^2=67%, P for heterogeneity 0.08) and low-dose CoQ10 (0.53 [-0.89–1.94], p-value 0.47, I^2=34%, P for heterogeneity 0.22) compared to placebo (0.24 [-0.93–1.41], p-value 0.69, I^2=39%, P for heterogeneity 0.18).

Similarly, the analysis showed no significant difference in the Total UPDRS score when comparing high-dose CoQ10 (0.51 [-1.09–2.10], p-value 0.53, I^2=0%, P for heterogeneity 0.47) and low-dose CoQ10 (0.86 [-0.52–2.24], p-value 0.22, I^2=0%, P for heterogeneity 0.59) versus placebo (0.71 [-0.33–1.75], p-value 0.18, I^2=0%, P for heterogeneity 0.82).

Discussion

This meta-analysis aims to determine the efficacy and safety of CoQ10 in slowing the progression of early Parkinson's Disease. Contrary to some animal and human studies providing evidence that CoQ10 inhibits progression of PD, this meta-analysis showed non-significant results in all components of the UPDRS scores. Several factors may underlie this difference. First, the heterogeneity of the study population might be contributory. In three studies initially considered in this meta-analysis, the severity of the Parkinson's Disease was not considered in the inclusion of the study.[16-17,19] The improvement seen in other studies might be attributed on the symptomatic treatment received by the study population and not on the intake of CoQ10 alone. Secondly, the difference in the dosages of Coenzyme Q10 used may also be a factor. In this meta-analysis, the dosages of CoQ10 used ranged from 300 to 2,400 mg/day.

This is the reason why the dosages were arbitrarily divided into high-dose and low-dose in the subgroup analysis, which still revealed non-significant results. Lastly, the UPDRS was used as the means of evaluation. However, it should be noted that the UPDRS is a tool which is still subject to the observer's judgment. In one study, the use of UPDRS revealed low inter-rater reliability in some of the items.[23] In another study, its use revealed a significant inter-rater variability even in trained health professionals.[24] Hence, a strong conclusion on the efficacy of CoQ10 cannot be established just by the assessment on UPDRS alone. The use of other objective tools to assess the improvement of medication on PD is highly recommended in future studies.

The strength of this meta-analysis is fourfold. First, a comprehensive search on CoQ10 was done. Several databases were searched and correspondence with many authors to clarify several studies were conducted. Secondly, the heterogeneity of the sample population was minimized. In order to remove the possible effect of a medication such as Levodopa on symptomatic PD as was observed in other studies, only studies involving patients not yet on any medication were included, hence the small number of included trials. Third, a subgroup analysis on high-dose and low-dose CoQ10 versus placebo was also presented. This allowed us to evaluate if there was any difference in the response of patients if given a particular dosage of CoQ10. And lastly, though the efficacy of the use of Coenzyme Q10 cannot be concluded, its safety can be secured. As shown in Table 3, there was almost no absolute difference in the occurrence of adverse drug events between CoQ10 and the placebo. Also, the withdrawal rates were also comparable. This supports previous studies indicating that CoQ10 has low toxicity and does not cause serious adverse effects. Moreover, it does not affect the endogenous biosynthesis of CoQ10 in the human body.[25] Gastrointestinal symptoms such as nausea, vomiting and constipation, which were noted in this meta-analysis, were the most common recorded adverse effects in literature even at the highest doses.[26]

Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

All the authors declared no conflicts of interest.

Funding Source

This paper was funded by the Philippine General Hospital Department of Neurosciences.

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