

COENZYME Q10 SUPPLEMENTATION FOR PROPHYLAXIS IN ADULT PATIENTS
WITH MIGRAINE : A META-ANALYSIS

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Abstrak

Objektif : Untuk mengenalpasti efek coenzyme Q10 (CoQ10) dalam penurunan tahap keterukan, kadar kekerapan serangan migrain dan durasi sakit kepala dikalangan pesakit yang menghadapi migrain.

Desain : ulasan sistematik dan meta analisis

Pencarian data : Cochrane Central Register of Controlled Trials, CENTRAL, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) dan Psychological Information Database (PsycINFO) daripada kajian paling awal sehingga Disember 2019.

Pemilihan kajian : Semua kajian klinikal terkawal rawak yang membandingkan CoQ10 dengan placebo atau digunakan sebagai ubat tambahan yang dimasukkan ke dalam meta analisis ini. Desain kajian bersilang dan klinikal terkawal sahaja tidak dimasukkan ke dalam meta analisis.

Olahan data : Heterogeniti pada nilai nominal dengan membandingkan populasi, tetapan, intervensi dan hasil akhir diukur dan heterogeniti statistik dinilai dengan menggunakan statistik I². Kesan rawatan untuk hasil dikotomi menggunakan nisbah risiko dan perbezaan risiko, dan untuk hasil berterusan, perbezaan min (MD) atau perbezaan min piawai; kedua-duanya dengan 95% CI telah digunakan. Analisis subkumpulan telah dijalankan untuk dos CoQ10 dan jika CoQ10 digabungkan dengan suplemen lain. Analisis sensitiviti digunakan untuk menyiasat risiko impak bias untuk penjanaan jujukan dan penyembunyian peruntukan kajian yang disertakan.

Keputusan : Enam kajian dengan sejumlah 371 peserta telah dimasukkan dalam meta-analisis. Tiada pengurangan ketara secara statistik dalam tahap keterukan sakit kepala

migrain dengan suplemen CoQ10. Suplemen CoQ10 mengurangi tempoh serangan sakit kepala berbanding dengan kumpulan kawalan (MD: -0.19; 95% CI: -0.27 hingga -0.11; kesan rawak; I2 statistik=0%; $p<0.00001$). Penggunaan CoQ10 mengurangi kekerapan sakit kepala migrain berbanding dengan kumpulan kawalan (MD: -1.52; 95% CI: -2.40 hingga -0.65; kesan rawak; I2 statistik=0%; $p<0.001$).

Kesimpulan : CoQ10 mempunyai kesan yang baik dalam mengurangkan tempoh dan kekerapan serangan migrain.

PROSPERO nombor pendaftaran CRD42019126127

ABSTRACT

Objective : To determine the effects of coenzyme Q10 (CoQ10) for reduction in the severity, frequency of migraine attacks and duration of headache in adult patients with migraine.

Design : Systematic review and meta-analysis.

Data sources : Cochrane Central Register of Controlled Trials, CENTRAL, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Psychological Information Database (PsycINFO) from inception till December 2019.

Study selection : All randomised control trials comparing CoQ10 with placebo or used as an adjunct treatment included in this meta-analysis. Cross-over designs and controlled clinical trials were excluded.

Data synthesis : Heterogeneity at face value by comparing populations, settings, interventions and outcomes were measured and statistical heterogeneity was assessed by means of the I^2 statistic. The treatment effect for dichotomous outcomes were using risk ratios and risk difference, and for continuous outcomes, mean differences (MDs) or standardised mean difference; both with 95% CIs were used. Subgroup analyses were carried out for dosage of CoQ10 and if CoQ10 combined with another supplementation. Sensitivity analysis was used to investigate the impact risk of bias for sequence generation and allocation concealment of included studies.

Results : Six studies with a total of 371 participants were included in the meta-analysis. There is no statistically significant reduction in severity of migraine headache with CoQ10 supplementation. CoQ10 supplementation reduced the duration of headache attacks compared with the control group (MD: -0.19; 95% CI: -0.27 to -0.11; random effects; I^2 statistic=0%;

p<0.00001). CoQ10 usage reduced the frequency of migraine headache compared with the control group (MD: -1.52; 95% CI: -2.40 to -0.65; random effects; I^2 statistic=0%; p<0.001).

Conclusion : CoQ10 appears to have beneficial effects in reducing duration and frequency of migraine attack.

Chapter 1

INTRODUCTION

1.1 INTRODUCTION

Migraine is an episodic disorder, the centrepiece of which is a severe headache generally associated with nausea and/or light and sound sensitivity. Migraine is a common disorder that affects up to 12% of the general population(1). Migraine is a debilitating brain disorder with serious social and financial consequences for the individual and the society(2). Migraine medications usually aim to reduce the frequency and intensity of headache attacks and few of the medications acts as preventive medication.

Low levels of the micronutrients such as riboflavin, magnesium and coenzyme in plasma and in the brain are reported in migraine patients(3). A deficit of these nutrients is thought to cause the migraine attacks. The cortical spreading depression is hypothesized to cause the elevation level of MMP-9 is associated with blood-brain barrier dysfunction and inflammation of nerves exacerbates migraine attacks(4, 5). The CoQ10, also known as ubiquinone, is one of the most important antioxidants that acts against hydrogen peroxide and other inflammatory markers of migraine along with reduction of expression cytokines and MMPs(6). CoQ10 is a vitamin-like compound, which can be synthesized by the body from phenylalanine and tyrosine. It has many roles in the body, especially in mitochondria and is thought to play a role in migraines, but the link is unknown(3). It acts as an important factor in the electron transport chain of mitochondria, which helps in energy metabolism and oxygen utilization in the brain and muscles(7). CoQ10 can be administered orally or parenterally. Peak blood levels occur 5–10 hours after oral administration. Elimination half-life is 33.19 hours(8). This meta-analysis aimed to determine the effectiveness of CoQ10 supplements as a prophylaxis for migraine in adult patients. The protocol for this meta-analysis is registered in International Prospective Register of Systematic review (PROSPERO) with trial number CRD42019126127, available from <https://www.crd.york.ac.uk/prospero>.

Chapter 2

OBJECTIVES OF THE STUDY

2.1. General Objectives

To assess severity of headache pain during attack, duration of migraine headache per month and frequency of migraine headache per month.

2.2 Specific Objectives

1. To look at numbers of days with nausea, numbers of analgesic used for headache
2. To look at numbers of acute migraine medication used
3. To look at quality of life and side effects of CoQ10 such as common cold symptoms, abdominal pain and soft faeces.

Chapter 3

MANUSCRIPT

3.1 TITLE

COENZYME Q10 SUPPLEMENTATION FOR PROPHYLAXIS IN ADULT PATIENTS WITH MIGRAINE : A META-ANALYSIS

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3.2 ABSTRACT

Objective To determine the effects of coenzyme Q10 (CoQ10) for reduction the severity, frequency of migraine attacks and duration of headache in adult patients with migraine.

Design Systematic review and meta- analysis.

Data sources Cochrane Central Register of Controlled Trials, CENTRAL, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Psychological Information Database (PsycINFO) from inception till December 2019.

Study selection All randomized control trials (RCTs) comparing CoQ10 with placebo or used as an adjunct treatment included in this meta-analysis. Crossover designs and controlled clinical trials (CCT) were excluded.

Data synthesis Heterogeneity at face value by comparing populations, settings, interventions and outcomes were measured and statistical heterogeneity was assessed by means of the I^2 statistic. The treatment effect for dichotomous outcomes were using risk ratios (RRs) and risk difference (RD), and for continuous outcomes, mean differences (MDs) or standardized mean difference (SMD); both with 95% confidence intervals (CIs) were used. Subgroup analyses were carried out for dosage of CoQ10 and if CoQ10 combined with another supplementation. Sensitivity analysis was used to investigate the impact risk of bias for sequence generation and allocation concealment of included studies.

Results Six studies with a total of 371 participants were included in meta-analysis. There is no statistically significant reduction in severity of migraine headache with CoQ10 supplementation. CoQ10 supplementation reduced the duration of headache attacks compared to the control group (mean difference -0.19, 95% CI -0.27 to -0.11; random effects; I^2 statistic =

0%; $P < 0.00001$). CoQ10 usage reduced the frequency of migraine headache compared to the control group (MD -1.52, 95% CI -2.40 to -0.65; random effects; I^2 statistic = 0%; $P = <0.001$).

Conclusion CoQ10 appears to have beneficial effects in reducing duration and frequency of migraine attack.

PROSPERO registration number CRD42019126127

3.3 INTRODUCTION

Migraine is an episodic disorder, the centrepiece of which is a severe headache generally associated with nausea and/or light and sound sensitivity. Migraine is a common disorder that affects up to 12% of the general population(1). Migraine is a debilitating brain disorder with serious social and financial consequences for the individual and the society(2). Migraine medications usually aim to reduce the frequency and intensity of headache attacks and few of the medications acts as preventive medication.

Low levels of the micronutrients such as riboflavin, magnesium and coenzyme in plasma and in the brain are reported in migraine patients(3). A deficit of these nutrients is thought to cause the migraine attacks. The cortical spreading depression is hypothesized to cause the elevation level of MMP-9 is associated with blood-brain barrier dysfunction and inflammation of nerves exacerbates migraine attacks(4, 5). The CoQ10, also known as ubiquinone, is one of the most important antioxidants that acts against hydrogen peroxide and other inflammatory markers of migraine along with reduction of expression cytokines and MMPs(6). CoQ10 is a vitamin-like compound, which can be synthesized by the body from phenylalanine and tyrosine. It has many roles in the body, especially in mitochondria and is thought to play a role in migraines, but the link is unknown(3). It acts as an important factor in the electron transport chain of mitochondria, which helps in energy metabolism and oxygen utilization in the brain and muscles(7). CoQ10 can be administered orally or parenterally. Peak blood levels occur 5–10 hours after oral administration. Elimination half-life is 33.19 hours(8). This meta-analysis aimed to determine the effectiveness of CoQ10 supplements as a prophylaxis for migraine in adult patients. Apart from that, we also looking into other potential medication that might improve the management of migraine and quality of life of patients. The protocol for this meta-analysis is registered in International Prospective Register of Systematic review (PROSPERO)

with trial number CRD42019126127, available from <https://www.crd.york.ac.uk/prospero>.

3.4 METHOD

Only randomized control trials (RCTs) comparing CoQ10 with placebo or as an adjunct treatment were accepted in the meta-analysis. All blinded and open-label studies were included in this meta-analysis. Crossover designs and controlled clinical trials (CCT) were excluded. We included the adult participants aged 18 till 50 years old of either sex or of any ethnicity. Supplementation with oral CoQ10 as monotherapy or in combinations with other dietary products, regardless in duration of therapy were included in the meta-analysis. Participants with migraine diagnosed by neurologist or physician according to either International Classification of Headache Disorder II (ICHD-II) or International Headache Society criteria (IHS) were included criteria for the meta-analysis. The primary outcomes and secondary outcomes in the trials that have been followed up for a minimum of 6 weeks after giving the interventions included in the meta-analysis. The study was actually followed the guidelines of PRISMA.

Identification of study

We searched the Cochrane Central Register of Controlled Trials, CENTRAL, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Psychological Information Database (PsycINFO) from inception till December 2019. We used the search terms “coenzyme Q10”, “ubiquinone” and “migraine” with Boolean operators of AND and OR (Refer Supplementary file 1). We checked the reference list of identifying RCTs and review articles to find unpublished trials or trials not identified by electronic searches. We contacted the experts in the field and pharmaceutical companies which market CoQ10 to identify unpublished trials. We searched for ongoing trials through the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), <https://www.who.int/ictcp/en/> and www.clinicaltrials.gov. We excluded trials published other

than the English language. We scanned the titles and abstracts from the searches and obtain full-text articles when they appear to meet the eligibility criteria, or when there was insufficient information to assess the eligibility. We assessed the eligibility of the trials independently and documented all the reasons for exclusion. We resolved any disagreements between the review authors by discussion. We contacted the authors if clarification is needed.

Data Collection and analysis

Three authors extracted data independently. We extracted data on the dosage and frequency of CoQ10 supplementation, criteria for diagnosis of migraine, age, sex, ethnicity, and the outcomes of each trials which include severity of the headache attacks, duration of headache in migraine attacks, frequency of migraine attacks in a month, numbers of days with nausea, numbers of analgesic used during headache attacks, numbers of acute migraine medication used, quality of life and adverse effects of CoQ10 using data extraction form. Disagreements between the review authors were resolved by discussion with the fourth author.

The Cochrane Collaboration's risk-of-bias tools was used to assess the risk of bias in of the included studies(9). Three authors assessed each trial's risk of bias independently. We assessed selection bias (randomisation, allocation concealment), performance bias (blinding of participant and health personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias (recall bias, transfer bias and etc). We resolved any disagreements by the discussion with the fourth author. We assessed the quality of evidence for primary and secondary outcomes, according to the GRADE methodology for risk of bias, inconsistency, indirectness, imprecision, and publication bias; classified as very low, low, moderate, or high(10).

We analysed data using Review Manager 5.3 software(11). We used random-effects model to pool data. We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by comparing populations, settings, interventions and

outcomes. Then, we assessed statistical heterogeneity by means of the I^2 statistic. We interpreted the heterogeneity as; 0% to 40% represent might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% would be considerable heterogeneity(9).

We measured the treatment effect using risk ratios (RRs) and risk difference (RD) for dichotomous outcomes and mean differences (MDs) or standardized mean difference (SMD); both with 95% confidence intervals (CIs) for continuous outcomes. We conducted subgroup analyses based on the different dosage of CoQ10 and if CoQ10 is combined with another supplementation. We explored the potential sources of heterogeneity when it is present. We checked all included trials for unit of analysis errors. Unit of analysis errors can occur when trials randomize participants to intervention or control groups in clusters, but analysed the results using the total number of individual participants. We adjusted results from trials showed unit of analysis errors based on the mean cluster size and intraclass correlation coefficient(9). We contacted the original trial's authors to request missing or inadequately reported data. We performed analyses on the available data if missing data are not available. We performed sensitivity analysis to investigate the impact of risk of bias for sequence generation and allocation concealment of included studies.

3.5 RESULTS

We retrieved 65 records from the search of the electronic databases and one record from other sources (Supplementary file 2, Figure 1). We screened a total of 60 records. We reviewed full text of 16 studies and excluded another 10 studies because all of the studies were non-randomized controlled trials(3, 12-20). Therefore, we included only six studies in this review.

We included six studies with a total of 371 participants(21-26). In all the trials, diagnosis of migraine was done based on International Headache Society criteria. Two out of

six studies (and one study that contributed to the primary outcome) declared funding from drug manufacturers(23, 26). Two out of six studies were multicentre trials in high-income countries(23, 26). Three studies involved a total of 167 female gender only as participants(21, 22, 25) and another three studies involved on both genders and a total of 204 participants(23, 24, 26). All the participants in the included studies were randomised into intervention and control groups. Three studies reported using CoQ10 with other elements such as multivitamin(23), L-carnitine(24) and preventive medication in the intervention group(21). One study used the medication in liquid formulation of water dispersed into nanoparticles (26), five studies used the medication in a capsule formulation(21-25). Different dosages of CoQ10 were administered in the studies: minimum of 30 mg per day(24), 300 mg per day(26), 400 mg per day(22), 600 mg per day(23), and 800 mg per day(21, 25). All six trials excluded any participants who on migraine preventive drugs in the last six months, who have history of using CoQ10 or other antioxidants supplementation for at least 3 months prior to the enrolment(21-26). One trial also excluded participants who failed to respond to the usage of more than two different prophylactic agents in the past or any patients who were resistant to all acute migraine drugs(23). All six included studies used placebo(21-26) and there was only one trial added the preventive migraine medication to the placebo(21); however, the preventive medication was used for both the intervention and control groups in this trial(21). Duration of CoQ10 treatment differs among the trials and was reported at 8 weeks in one study(24), and at 3 months in five other studies(21-23, 25, 26). Table 1 summarised the characteristics of the included trials.

All six included trials followed-up the participants for a minimum of six weeks(21-26). Six studies were included in analyses of the primary outcomes(21-26). We also analysed according to subgroup by dosage of more and less than 400 mg of CoQ10. Secondary outcomes reported in the three trials(21, 23, 26). One study reported using several questionnaires for assessing quality of life affected by migraine(21), which were headache impact test (HIT-6) and migraine specific quality of life (MSQ) questionnaires to assess wellbeing and daily

functioning; meanwhile migraine disability assessment (MIDAS) questionnaire to assess disability caused by migraine. The HIT-6 used scoring of 36–49 with higher scores indicate more severe effect of migraine, the MSQ reported the scores between zero and 100 with higher scores indicate better quality of life and the MIDAS reported the scores between zero and 35 with higher scores indicate severe disability(21). We excluded 10 studies and all of the studies are non-randomized controlled trials(3, 12-20).

Risk of bias

Assessment risk of bias is shown in Figure 2a and Figure 2b (Refer Supplementary file 3, Figure 2a and Figure 2b). The proportion of studies assessed as low, high or unclear risk of bias for each risk of bias domain is presented in Figure 2a (Refer Supplementary file 3, Figure 2a). Detection bias domain had 50% of low risk with attrition and reporting bias domains around 80% of low risk. The risk of bias summary for individual studies is showed in Figure 2b (Refer Supplementary file 3, Figure 2b). Three studies had unclear risk for detection bias (21, 25, 26) and for attrition and reporting bias, only one trial had high risk of bias(23).

All six studies described the method of randomisation used and randomised the participants according to block randomization(21-26). Allocation concealment was mentioned in all six included studies(21-26). All six studies mentioned about blinding the personnel and the participants(21-26). All six studies had less than 20% lost to follow-up and the reasons such as major protocol violation(23), refused to continue the study(25, 26), failed to return to clinic(21, 22), pregnancy(21, 22, 24) and failed to keep diary(21, 22) and there were balanced between both groups. Only one study carried out an intention-to-treat analysis in which the participants were analysed according to the groups that they were initially assigned(21). All six studies reported the outcomes as specified in their methods section(21-26). We detected no other potential sources of bias.

Effects of interventions

All six studies measured the primary outcomes and assessed at three months post intervention(21-26). Three studies measured the secondary outcomes(21, 23, 26). Three studies did not state on the assessment of outcomes(21, 25, 26).

Primary outcomes

All six included studies reported severity of headache during migraine attack after taking CoQ10 for at least six weeks(21-26). The meta-analysis found no significant reduction in severity of headache with CoQ10 (MD -1.33, 95% CI: -2.97 to 0.31; I^2 statistic = 99%; $P = 0.110$; 6 trials; 371 participants) (Refer Supplementary file 3, Figure 3). With more than 400 mg (MD -1.33, 95% CI -2.75 to 0.08, random effects; I^2 statistic = 0%; $P = 0.07$; 3 trials; 167 participants) or less than 400 mg per day of CoQ10 (MD -1.27; 95% CI -3.42 to 0.89; random effects; I^2 statistic = 100%; $P = 0.25$; 3 trials; 204 participants), there is no difference in the severity of headache compared to the control group.

All six studies reported on the duration of headache attacks per month(21-26). There was significant reduction of duration of headache attacks with CoQ10 as compared to the control group (MD -0.19, 95% CI -0.27 to -0.11; random effects; I^2 statistic = 0%; $P < 0.00001$; 6 trials, 371 participants) (Refer Supplementary file 3, Figure 4).

Five studies reported on the frequency of migraine headache per month(21, 22, 24-26). There was significant reduction in the frequency of migraine headache with the CoQ10 as compared to the control group (MD -1.52, 95% CI -2.40 to -0.65; random effects; I^2 statistic = 0%; $P = <0.001$; 5 trials, 259 participants) (Refer Supplementary file 3, Figure 5).

a) Secondary outcomes

One study reported on the number of days with nausea due to migraine headache during the study period(26). The CoQ10 supplementation reduced the number of days with nausea due to migraine headache (MD -1.70; 95% CI -2.92 to -0.48; $P = 0.006$; 1 trial, 42 participants). No other study reported on this outcome. The same study reported the number of acute migraine

medications usage during the study period(26). The CoQ10 supplementation reduced the number of acute migraine medications usage (MD 0.02; 95% CI -0.42 to 0.46; P = 0.91; 1 trial, 42 participants)(26).

Only one trial measured the quality of life among patients with migraine headache(21). Three types of questionnaire including Migraine-specific quality of life (MSQ), The Headache Impact Test (HIT-6) score and Migraine Disability Assessment (MIDAS) score were used to measure the impact of the treatment on migraine headache on quality of life(21). Migraine-specific quality of life (MSQ) questionnaire reported on role restrictive, role preventive and emotional functioning. There were no significant improvements in MSQ questionnaire on role restrictive (MD 17.85; 95% CI 9.59 to 26.11; P < 0.0001; 1 trial, 77 participants), role preventive (MD 17.16; 95% CI 8.75 to 25.57; P < 0.0001; 1 trial, 77 participants) and emotional functioning (MD 16.68, 95% CI 6.70 to 26.66; P = 0.001; 1 trial, 77 participants) with the CoQ10 supplementation. The CoQ10 supplementation showed improvement in The Headache Impact Test (HIT-6) score (MD -4.29; 95% CI -7.19 to -1.39; P = 0.004; 1 trial: 77 participants) and improvement in Migraine Disability Assessment (MIDAS) score (MD -6.00; 95% CI -9.93 to -2.07; P = 0.003; 1 trial: 77 participants). One trial reported on the adverse effects outcome on diarrhoea (OR 4.44; 95% CI 0.90 to 21.79; P = 0.07) and chromaturia (OR 19.45; 95% CI 1.10 to 344.70; P = 0.04)(23) and they not different in the CoQ10 group.

3.6 DISCUSSION

Summary of main results

This review was designed to include all RCTs addressing the effectiveness of CoQ10 as one of the alternative medications for migraine prophylaxis. There was significant reduction in the duration of migraine by 0.19 point and the frequency of migraine by 1.52 point during the follow-up. Meanwhile, there was no significant reduction in severity of headache during attack