Original Article

Potential Effect of Coenzyme Q10 (Ubiquinone) on Serum NGAL Biomarker and Kidney Function Following Coronary Artery Bypass Grafting Surgery

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Abstract

Background: Acute kidney injury (AKI) is a common complication after coronary artery bypass grafting (CABG) surgery, and is associated with major adverse outcomes. The effect of preoperative administration of coenzyme Q10 was evaluated to realize that whether it could prevent the occurrence of AKI following elective CABG surgery.

Materials and Methods: Two hundred and fifty patients who were a candidate for elective CABG surgery between September 2017 and August 2018 were randomly assigned to intervention group (receiving coenzyme Q10, 300 mg BID for 2 days before surgery) and control group. Serum NGAL (neutrophil gelatinase-associated lipocalin) was measured at baseline, 6, and 24 hours after surgery. Serum creatinine (sCr) and urine output (UO) were also measured at baseline and after surgery.

Results: Fifty patients completed the study. The total incidence of acute kidney injury was 32%. There were no significant differences in the incidence of AKI (p=0.07) between the two groups. Serum NGAL was shown no significant difference at 6 (p=0.13) and 24 (p=0.22) hours after surgery compared to the baseline level between the two groups, whereas, the significant difference in the hospitalization duration was shown between them (p=0.02).

Conclusion: CoQ10 supplementation did not significantly decrease the incidence of AKI in patients undergoing elective CABG.

Keywords: Ubiquinone, Coenzyme Q10, Acute kidney injury, Coronary artery bypass grafting surgery, Neutrophil gelatinase-associated lipocalin protein

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Introduction

Acute kidney injury is a complication, which occurs frequently in post-cardiac surgery cases and can be linked to increased morbidity and mortality (1). It is also true that cardiac surgery is the second most common cause of AKI in intensive care units (ICU) (2). Overall mortality after open-heart surgery could be as high as 8% and among patients who develop severe AKI who are in need to dialysis, it can reach up to 88% (3).

Pharmacological interventions may be considered to reduce the occurrence of renal injury in patients without evidence of acute renal dysfunction as primary prevention (4). There is a growing body of evidence suggesting a detrimental role of free oxygen radical species in the development of AKI (5). The beneficial role of endogenous and synthetic antioxidants in the prevention of AKI has been demonstrated in animal and cell-based models (6).

However, the data regarding the renal protective effect of synthetic antioxidant supplementation in human AKI and renal diseases are more ambiguous (7). Coenzyme Q10 (CoQ10) may have the potential for preventing and treating cardiovascular disease, improving cardiac function, and decreasing oxidative stress in patients with renal impairment (8). CoQ10 supplementation improves glycemic control and vascular dysfunction in type II diabetes, enhances renal function in patients with chronic kidney disease, and reduces inflammation. The beneficial role of supplemental CoQ10 may be considered as a result of cellular energy generation, antioxidant, and anti-inflammatory properties (9). Coenzyme Q10 (CoQ10) has been used as an antioxidant to prevent AKI in patients (10). However, no published study has systematically and comprehensively summarized the renoprotective effect of CoQ10 after CABG. This study aimed to examine the prophylactic effect of CoQ10 on acute kidney injury in post-CABG patients.

Methods

After receiving approval from the University Ethics Committee and obtaining written informed consent (ethics code: IR.SBMU.PHNM.1394.311), fifty adult patients who underwent elective CABG at a teaching hospital were recruited for this randomized control trial. Exclusion criteria for the study were as follows: patients who needed emergency CABG, high-risk patients such as those who needed concurrent valvular surgery and CABG, presence of known drug allergy to CoQ10, history of chronic kidney disease (stage IV and V), preoperative creatinine clearance less than 30 ml/min and history of chronic hepatic disease (liver function test three times the upper limit).

Using a computer-based randomization method, the patients in the intervention group received CoQ10, 300 mg tablet, twice a day, for 2 days before the surgery (n=25). Patients in the control group did not receive CoQ10. The same routine treatment regimen was administered in both groups.

Patients underwent standard intravenous anesthesia as follows: All patients were premedicated with lorazepam of 2 mg orally and morphine of 0.15 mg/kg intramuscularly 2h and 30 min before surgery respectively. Anesthesia was induced by fentanyl of 5 mcg/kg, thiopental of 3 mg/kg and atracurium of 0.5 mg/kg and was maintained with fentanyl 1–2 mcg/kg/h, propofol 50-70 mcg/kg/min and atracurium 10 mcg/kg/h. All patients received heparin 300-400 IU/kg before CPB (Cardiopulmonary bypass) to achieve an activated clotting time (11) of more than 480 sec. Surgery was done according to standard on-pump and mild hypothermia. During CPB, to achieve the target ACT, additional heparin was prescribed, and after the separation from CPB and heparin neutralization, protamine sulfate (1 mg per 100 units of heparin) was given to reach the targeted ACT level (80–120 sec).

Patients have received epinephrine infusion after CPB when SBP was less than 90mmHg and they were paced regarding keep HR more than 70/min. All patients were transferred to the intensive care unit (ICU) and received mechanical ventilation with synchronized intermittent mandatory ventilation (SIMV) and pressure support (PS) mode after surgery and in the ICU. They were weaned and extubated during the first hours after arrival according to the standard weaning protocol.

During preoperative hospitalization, laboratory values such as complete blood count (CBC), sodium, potassium, magnesium, calcium, phosphorus, albumin, urea, serum creatinine, and blood sugar were measured daily. Postoperative arterial blood gases (ABG) and lactate were measured within the first 24 hours if required, while urine output was measured hourly during ICU stay. Patients were transferred to the cardiac care unit (CCU) on day 2 after surgery based on the following criteria: being hemodynamically stable with acceptable oxygenation and ventilation, being conscious, having no life-threatening arrhythmias, active bleeding, electrolyte abnormality, delirium, and severe anemia (Hgb <8 g/dL). A urinary catheter and pericardial drain were removed before patients were transferred to CCU.

AKI based on acute kidney injury network (AKIN) classification was defined as abrupt (within 48 h) increase in serum creatinine of 0.3 mg/dL or more (≥26.4 μmol/L) or a percentage increase in serum creatinine of 50% or more (1.5-fold from baseline) or reduction in urine output (documented oliguria of < 0.5 mL/kg/h for >6 h) (12). Recovery from AKI was defined as the return of serum creatinine or glomerular filtration rate to the baseline value. Neutrophil Gelatinase-associated Lipocalin was used to evaluate renal function. Serum NGAL was measured by enzyme-linked immunosorbent assay (13) at baseline and 6 and 24 hours following surgery. Serum creatinine (sCr) was measured at baseline and then 24, 48, and 72 hours post operatively. As a secondary outcome, C reactive protein (CRP) was measured by hs-CRP before and 24 hours after CABG.

The categorical variables were presented as percentage and continuous variables were compared using the Student's t-test for normally distributed values and the Mann–Whitney U test for non-normally distributed variables. Proportions were compared using the Chi-square test. Statistical analysis was performed using SPSS® version 24 (IBM SPSS, Chicago, IL, USA). Statistical significance was considered as $p<0.05$.

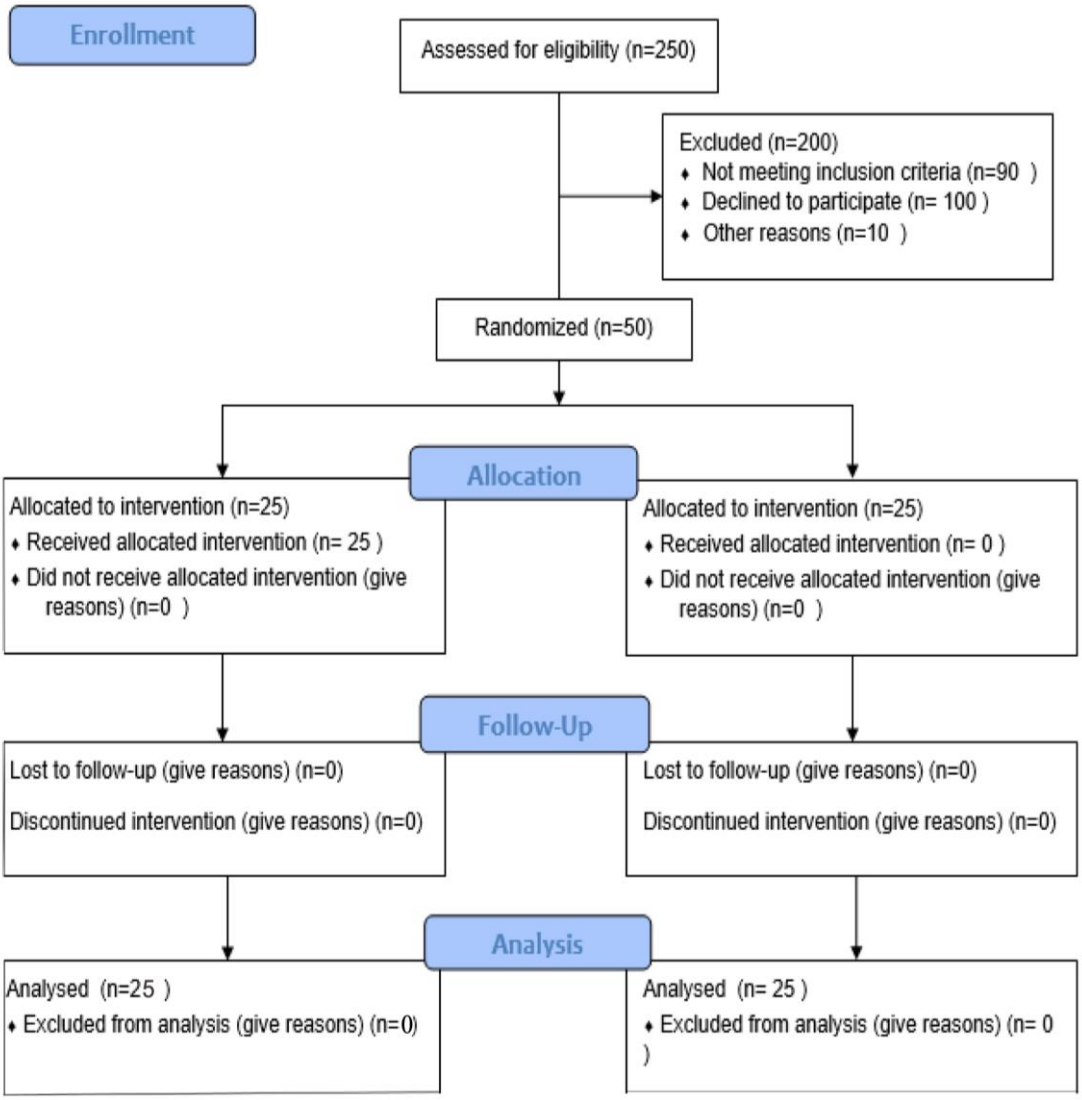

Figure 1. CONSORT flow diagram.

Results

Fifty patients with a mean age of 59.3±9.88 (ranging from 50 to 70) years completed the study. Of these patients, 37 were males and 13 were females. One patient died in the control group (Figure 1).

Differences between the two groups in terms of demographic data (age, sex, BMI) comorbidities (diabetes, hypertension), cardiovascular status, and the number of grafts were not statistically significant (Table 1). Moreover, there were no significant differences among patients' duration of surgery, duration of ischemia, and pump time (Table 2).

Based on AKIN criteria, AKI was seen in 32% of patients with no clinically significant difference in incidence, severity, and duration of AKI between the two groups. The incidence of CABG associated AKI was 20% and 44% in CoQ10 and control groups, respectively (p=0.07). The NGAL baseline levels were not statistically significant between the two groups (94.92±81.46 in the CoQ10 group versus 125.37±117.07 in the control group, p=0.8).

Fluctuation in serum creatinine levels between the two groups was evaluated at 24, 48, and 72 hours postoperatively. Results demonstrated a larger change in postoperative sCr levels for the control group but were not clinically significant (Table 3).

Measurements of NGAL at 6 and 24 hours after CABG showed no clinically significant changes between the two groups (-64.76±45.53 in CoQ10 group versus -113.33±46.37 in the control group, p=0.13; -54.96±51.67 in CoQ10 group versus -109±117.53 in the control group, p=0.22, respectively). Moreover, assessment of sCr, U/O, and CRP levels after surgery revealed no statistically significant differences between the two groups (Table 3).

As shown in table 4, There were no significant differences in the duration of mechanical ventilation (p=0.1) and the ICU length of stay (p=0.99) between the two groups. Duration of hospitalization was considerably shorter in the CoQ10 group (p=0.02). Data regarding CVP, BP, Hgb, Hct, BUN, and Alb are provided as well in Table 4.

Discussion

Fluid balance optimization, establishing adequate perfusion, and avoidance of nephrotoxic drugs (Diuretics, ACE inhibitor/ARBs, NSAIDs) are amongst strategies that can be used to avoid renal complications (14). Several drugs, including N-acetyl cysteine, have been used to prevent AKI after cardiac surgery; however studies failed to demonstrate their effectiveness (15). Many studies have evaluated the effect of novel renoprotective drugs, namely

Table 1: Demographic data and clinical characteristics.

Variable	CoQ10 group (N= 25)	Control group (N=25)	P value
Age (year)	64.92±8.70	60.88±9.76	0.11
Sex (male)	16(64%)	21(84%)	0.11
BMI (kg/m^2)	25.76±3.35	26.45±3.79	0.69
BSA (m^2)	1.76±0.15	1.78±0.21	0.5
Diabetes	10(40%)	6(24%)	0.23
Hypertension	8(32%)	6(24%)	0.53
EF(%)	44.60±7.89	43.96±8.48	0.83
3VD	17(68%)	18(72%)	0.76

BMI: Body Mass Index, BSA; Body Surface Area, EF: Ejection Fraction, 3VD: Three-vessel disease

Table 2: Surgical factors data.

Variable	CoQ10 group (N=25)	Control group (N=25)	P value
Operation time (minutes)	236.8±34.09	263.32±61.43	0.06
Pump time (minutes)	72.36±17.29	85.36±30.19	0.07
Ischemic time (minutes)	44.28±12.25	56.16±30.73	0.23

Table 3: Assessment of renal function in patients.

Variable	CoQ10 group (N=25)	Control Group (N=25)	P value
Baseline NGAL (ng/ml)	94.92±81.46	125.37±117.07	0.8
NGAL changes 0-6 h	-64.76±45.53	-113.33±46.37	0.13
NGAL changes 0-24 h	-54.96±51.67	-109±117.53	0.22
Baseline sCr (mg/dl)	1.07±0.26	1.24±0.23	0.02
sCr changes 0-24 h	-0.078±0.26	-0.20±0.38	0.21
sCr changes 0-48 h	-0.05±0.17	-0.17±024	0.07
sCr changes 0-72 h	-0.07±0.18	-0.15±0.23	0.14
U/O changes 0-6 h	688.04±473.12	545±751.82	0.48
U/O changes 0-12 h	1725.4±852.97	1505±1010.75	0.41
U/O changes 0-24 h	2970±931.07	2997±1400.78	0.6
Baseline CRP (mg/l)	16.06±12.33	14.86±14.12	0.41
CRP changes 0-24 h	-39.61±15.94	-41.08±12.86	0.32

NGAL; neutrophil gelatinase-associated lipocalin, CRP: C-Reactive Protein, sCr: Serum creatinine, U/O: Urine Output

dopamine, fenoldopam, calcium channel antagonists, natriuretic peptides, and diuretics, although the results of these studies might not be much reliable because of the poor quality of these studies (16). Moreover, to inspect the beneficial role of antioxidants in the prevention of AKI following cardiac surgery, several studies investigated the impact of preoperative administration of antioxidants such as selenium and vitamin C. These studies revealed that preoperative administration of vitamin C and selenium was not effective in preventing AKI and associated morbidity and mortality after coronary artery bypass graft surgery (17, 18). Our study revealed that CoQ10 as a preventive measure seems to have no effects on the occurrence of AKI in patients following CABG. The results regarding postoperative AKI incidence and NGAL measurements showed no significant differences between CoQ10 and the control group.

Table 4: Secondary outcomes analysis.

Variable	CoQ10 group (N=25)	Control group (N=25)	P value
Mechanical Ventilation Duration (day)	4.84±0.89	4.12±2.12	0.10
Baseline CVP (mmHg)	10.12±2.50	10.56±4.86	0.64
CVP before CABG (mmHg)	12.75±3.26	11.47±3.64	0.22
CVP 6h after CABG (mmHg)	14.04±3.04	11.88±3.91	0.04
CVP 24h after CABG (mmHg)	14.08±3.17	13.48±3.58	0.31
Hospitalization Duration (day)	8.32±1.79	10.6±3.69	0.02
Length of Stay in ICU (day)	4.72±1.42	4.68±1.28	0.99
BP systolic baseline (mmHg)	110.83±8.23	118.17±13.98	0.06
BP systolic change 0-24	3.5±9.71	-15.62±33.85	0.02
BP Diastolic baseline (mmHg)	71.55±13.84	80.77±11.39	0.04
BP Diastolic change 0-24	0.87±8.5	-11.08±17.80	0.03
Hgb baseline (g/dl)	13.80±2.05	14.27±1.47	0.37
Hgb change 0-24	-2.64±2.17	-3.34±1.48	0.19
Hct baseline (%)	40.16±5.15	41.78±3.87	0.21
Hct change 0-24	-7.74±4.37	-9.39±4.46	0.19
BUN baseline (mg/dl)	34.24±10.17	36.48±13.27	0.81
BUN change 0-24	1.85±11.66	-4.29±12.10	0.08
Alb baseline (g/dl)	3.76±0.83	3.72±0.67	0.87
Alb change 0-24	-0.39±1.54	-0.41±0.76	0.96

CVP: Central Venous Pressure, ICU: Intensive Care Unit, BP: Blood Pressure. Hgb: Hemoglobin

AKI is characterized by abrupt deterioration in kidney function, the diagnosis of which depends on serum creatinine measurements. Early detection and timely treatment are the keys to the successful treatment of AKI (19). Unfortunately, creatinine is a delayed and unreliable indicator of AKI (20). Nevertheless, understanding the early stress response of the kidneys to acute injuries has revealed several potentially useful biomarkers (21). The discovery, translation, and validation of NGAL, a sensitive and specific early marker of AKI, arguably is the most promising novel AKI biomarker that has been examined and analyzed (22, 23). NGAL is emerging as an excellent standalone troponin-like biomarker in the plasma and urine with the aim of AKI prediction, clinical trials monitoring in AKI cases and the prognosis of AKI in several common clinical scenarios (24). The protective effect of CoQ10 for AKI has been

proposed for its antioxidant effects (25, 26). Large population-based studies have supported that CoQ10 supplementation attenuates gentamicin-induced renal injury via decreasing necrotic tubule rate and hyaline accumulation in tubule (27). Takenaka et al proposed that coenzyme Q10 could have protective effects on AKI in warm ischemic injuries of the animal models(28). Likewise, Akira Ishikawa suggested the therapeutic effects of Ubiquinol, which may be a candidate for the treatment of patients with kidney disease (29). However, their findings were inconclusive. Unfortunately, these previous findings were not confirmed by our study. To our knowledge, this is the only study exploring the protective effect of CoQ10 in the prevention of AKI following cardiac surgery in humans. Our results are consistent with other reports that suggested CoQ10 was not effective in reducing renal damage (30, 31). In contrast, an original article demonstrated the protective effect of CoQ10 against free radical oxidative damage which can harm kidney function after CABG (32). A systematic review and meta-analysis was performed to elucidate the role of CoQ10. Favorable effect of CoQ10 was revealed when considered as a prophylactic treatment for preventing complications in patients undergoing cardiac surgery with cardiopulmonary bypass. However, high-quality randomized controlled trials are required to clarify this role (10). The administration of CoQ10 in the prevention of contrast-induced nephropathy (CIN) after coronary angiography has been associated with different results (33). None of the patients in this study required renal replacement therapy during hospitalization. This study had a few limitations as well. Firstly, because of the high cost and resource limitations of parenteral CoQ10 in our institution, we used oral forms of the medication, which has a different bioavailability compared to its parenteral form. Furthermore, the small sample size might have precluded our results from being significant. Therefore, our results cannot be extrapolated to high-risk patients or those undergoing emergency CABG. We would recommend further studies with larger sample size.

As patients with a history of chronic kidney disease and valvular heart disease, the two main risk factors contributing to AKI incidence, were excluded from the study (34); the results obtained in this study could not be extrapolated to this population.

Occasionally asymptomatic acute kidney injury may happen in patients after their discharge from the hospital (35). Considering the follow-up duration in this study that was during the patient's hospital stay, some cases may have been missed in our research.

Finally, further studies with different doses and administration duration of CoQ10 as well as analyzing other AKI biomarkers such as IL-18, KIM-1, L-FABP, and Cystatin-C are recommended.

Conclusion

In conclusion, we found that the preoperative administration of CoQ10 could not reduce the incidence of AKI and its associated morbidity and mortality in patients undergoing CABG. Further high-quality RCTs are needed to clarify the potential prophylactic effect of CoQ10 on surgery-related AKI.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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