Preoperative C-Reactive Protein Levels Predict Readmission Following Elective Vascular Surgery

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Abstract

Background

C-reactive protein levels (CRP) may be reduced with long-term administration of ubiquinol (CoQ₁₀) in patients with chronic ischemic heart disease but the impact of a short-term period of administration in patients undergoing elective vascular surgery is uncertain.

Methods

A double-blind randomized controlled trial was implemented to determine whether preoperative administration of CoQ₁₀ could reduce cardiac biomarker elevations. Patients were randomly assigned to CoQ₁₀ (400 mg per day) versus Placebo for 3 days prior to surgery. BNP, troponin and CRP were obtained pre and post-surgery. The primary endpoint was peak BNP and secondary endpoints were length of stay and readmission.

Results

One hundred and twenty-three patients were randomly assigned to CoQ₁₀ (N=62) or Placebo (N=61) for 3 days pre-surgery. At 24 hours post-surgery, the group receiving CoQ₁₀ had lower BNP levels with no intergroup differences in CRP. Within 1-year post-discharge, thirty-six (29%) were readmitted and preoperative risk for readmission (HR: 95% CI) included diabetes mellitus (3.60: 1.46-8.91), active smoking (3.55: 1.43-8.78) and CRP (1.35: 1.04-1.76). C-index for all three variables predicting readmission was 0.727.

Conclusions

Short-term administration of CoQ₁₀ reduced perioperative BNP but not CRP levels. CRP, along with diabetes and active smoking were independent predictors of readmission and should be targeted as a means of reducing subsequent rehospitalizations following elective vascular procedures.

Trial Registration

clinicaltrials.gov Identifier: NCT03956017

Introduction

Among Medicare Beneficiaries undergoing vascular surgery, nearly 1 in 4 patients are readmitted within 30 days of hospital discharge and as a DRG-related cause of readmission is second only to congestive heart failure (1). Although readmissions following vascular surgery are often unplanned (2, 3), identifiable clinical risk factors can be recognized at the time of discharge and include age, socioeconomic factors and select comorbidities (4-9). There is emerging interest in exploring the utility of perioperative biomarkers as a means of predicting those patients who have the highest risk of adverse
postoperative outcomes, including unplanned readmissions (10). Preoperative NT Pro-BNP has been recommended as an optimal means of risk-stratifying patients undergoing non-cardiac operations (11) and has been shown to have value in patients undergoing vascular surgery (12). In support of those studies, we have shown that preoperative NT pro-BNP levels predict postoperative risk of myocardial injury and of interest, can be reduced following surgery with preoperative administration of ubiquinone (CoQ₁₀) (13). C-reactive protein, a readily available biomarker can also predict poor outcomes in patients with ischemic heart disease (14, 15) and together with BNP, may have value in predicting adverse events in patients with vascular disease (16, 17). In the present study, we did additional analyses to assess the utility of CRP levels in predicting risk of readmission to the hospital following hospital discharge. Because long-term administration of ubiquinone (CoQ₁₀) has been shown to reduce CRP levels in selected patients (18, 19), testing the effects of a short-term period of administration on postoperative CRP levels is relevant.

**Methods**

The Human Studies Subcommittee of the Research and Development committee at the Minneapolis VA Medical Center approved this study. All patients were screened at their preoperative vascular clinic within 4 weeks of a scheduled operation. Inclusion criteria for eligible patients was a clinical indication for an elective vascular operation. Exclusion criteria included emergent or urgent need for vascular surgery, known allergic reaction to CoQ₁₀ or participation in another research project. Individuals who met the inclusion and exclusion criteria were offered participation in the trial and given informed consent. The design was a randomized controlled double-blind trial.

*Randomization and Assignment of Treatment*

The methodology of the primary trial results has been previously published (13) and is summarized in Figure 1. Following informed consent, patients were referred to a research pharmacist and treatment was randomly designated in a blinded fashion, with permuted blocks. Tablets of either Ubiquinone (CoQ₁₀) or placebo were prepared according to assigned treatment without identifiers of the medication. The prepared medication was provided to the patients by pharmacy, with instructions to take 2 tablets per day for 3 days prior to surgery. The rationale for 3 days of therapy, relates to the logistics of when patients are seen prior to their elective procedure and the feasibility of executing a trial within the time frame of the operation. The dose of 400 mg per day was chosen, based on prior clinical studies and the observation that plasma levels peak at 6 hours, and remain increased for 33 hours (20). The research coordinator confirmed that patients took all medications as prescribed. The research coordinator followed the patients throughout the hospitalization period and recorded clinical events within 1 year following discharge.

*Elective Surgery and Outcomes*
Patients were admitted to the surgical floor, either the night before or the day of the surgery. Blood was obtained for baseline preoperative cardiac biomarkers, including NT-Pro BNP, troponin I and high sensitivity C-reactive protein and repeated daily at 24 hours and 48 hours, if the patient remained in the hospital. NT-Pro BNP and troponin I levels were considered abnormal, if they exceeded the upper reference limit (URL) of the specific assay. Management of the patients were done by the surgical team, and consultative cardiologists, as needed, without any knowledge of assigned treatment. No cases were cancelled or delayed because of abnormal cardiac biomarker measurements. Blood was obtained from each patient for the analysis of troponin I, C-reactive protein and NT-Pro BNP. Baseline lab was obtained either on the morning of the surgery, or the night before, if the patient was lodging. The research coordinator confirmed that each subject had taken their assigned drugs for the 3 days prior to the operation. Blood assays were repeated each day following the operation for up to 48 hours. The upper reference limit (URL) of each assay was used, based on the manufacture's guidelines for that specific assay. The primary end-point measure was NT-Pro BNP levels at 24 hours following surgery (13). In this paper, we have focused on clinical variables that predicted a secondary end-point measure, which was readmissions within 1 year following hospital discharge.

Statistical Analysis

Data are expressed as either means and SD or median and Interquartile when specified. All clinical variables were obtained, including biomarker levels at baseline and following surgery. Biomarker levels were also expressed as exceeding the URL of each specific assay and categorized as the incidence of elevated values. Intergroup differences between patients randomized to CoQ$_{10}$ versus Placebo were tested by Student's t-test, with significance set at the $P<0.05$ level for comparing continuous variables. For categorical variables, chi-square tests were utilized. Among data that was not normally distributed, non-parametric testing was performed to confirm those findings, using a Wilcoxon 2 sample test. Readmissions to the hospital were categorized according to diagnoses and time from discharge. All clinical variables were compared between those patients with and without readmissions. A multivariate logistic regression model was then done, entering all univariate variables that had a $P \leq 0.10$ into the model, to determine independent predictors of readmission. Nonsignificant variables and are left with the three clinical variables that predicted readmission.

Results

Among all patients, preoperative cardiac risks included a history of ischemic heart disease (N=52), congestive heart failure (N=12), stroke (N=23) and diabetes mellitus (N=48) and the planned vascular procedures were infra-inguinal (N=78), carotid (N=36), and intraabdominal (N=9). There were no intergroup differences in these clinical variables according to the assigned treatment. At 24 hours following surgery, median NT Pro-BNP levels (Interquartile) in the treatment and placebo groups were 397 (211-686) and 591 (288-1433) pg/ml respectively ($P<0.01$) while median CRP levels were 21 (12-40) and 20 (10-41) mg% respectively ($P=0.83$). Peak median post-operative troponin I levels (interquartile) were 0.040 (0.024-0.111) ng/ml in the CoQ$_{10}$ treated and 0.052 (0.029-0.141) ng/ml in the placebo groups.
During the hospitalization, there were no in-hospital deaths and a postoperative myocardial infarction was diagnosed in four patients (2 patients from the CoQ₁₀ group and 2 patients from the placebo group). Total length of stay was 3.05±3.17 days in the CoQ₁₀ group and 3.71±3.74 days in the placebo treated group (P=0.29).

Thirty-six (29%) of the patients were readmitted to the hospital within 1 year of hospital discharge following their elective surgery and the diagnosis at the time of readmission was related to an infection in 13 patients, 9 of which occurred within 30 days of the original hospital discharge (Figure 2). Table 1 shows all the bivariate relationships for clinical variables in patients with univariate predictors for readmission to the hospital and Figure 3 shows the independent risks produced from a multivariate logistic regression model. This model was shaved down twice, once by only taking bivariate predictors with a P value of 0.10 or lower and then subsequently removing those variables that were not significant (ODDS RATIO: 95% Confidence Intervals) including diabetes mellitus (3.60: 1.46-8.91), active smoking (3.55: 1.43-8.78) and elevated preoperative C-reactive protein (1.35: 1.04-1.76). C-index for all three variables predicting readmission was 0.727.

Table 1: Characteristics of patients with and without readmissions following discharge
| Clinical Characteristics                  | Readmits (+) | Readmits (-) | P-Value |
|------------------------------------------|-------------|--------------|---------|
|                                          | N=36        | N=87         |         |
| **Preoperative Variables**               |             |              |         |
| Preoperative CoQ_{10} Administration     | 58%         | 47%          | P=0.27  |
| Age (years)                              | 68±8        | 70±9         | P=0.27  |
| History of Ischemic heart disease        | 44%         | 41%          | P=0.76  |
| History of congestive heart failure      | 17%         | 7%           | P=0.10  |
| History of TIA or Stroke                 | 19%         | 18%          | P=0.89  |
| History of Diabetes Mellitus             | 55%         | 31%          | P<0.01  |
| Insulin-Dependent Diabetes Mellitus      | 11%         | 8%           | P=0.59  |
| Creatine ≥ 2.0 mg%                       | 3%          | 3%           | P=0.85  |
| Active Smoker                            | 61%         | 35%          | P<0.01  |
| Revised Cardiac Risk Index               | 1.9±0.9     | 1.8±0.8      | P=0.35  |
| Abnormal LV Function (LVEF <55%)         | 29%         | 35%          | P=0.54  |
| C-reactive protein @ baseline (mg%)*     | 3.5 (2.1-9.1) | 2.9 (1.2-5.6) | P<0.01  |
| NT Pro-BNP @ baseline (pg/ml)*           | 200 (105-540) | 194 (85-361) | P=0.15  |
| Troponin I @ baseline (µg/ml)            | 0.004±0.011 | 0.005±0.018 | P=0.76  |
| LDL cholesterol (mg%)                    | 68±26       | 73±34        | P=0.37  |
| Triglyceride (mg%)                       | 181±114     | 184±141      | P=0.93  |
| HgbA1c (%)                               | 6.7±1.3     | 6.5±1.4      | P=0.55  |
| **Perioperative Variables**              |             |              |         |
| Rest pain or Tissue Loss                 | 17%         | 21%          | P=0.61  |
| Abdominal Aortic Surgery                 | 5%          | 8%           | P=0.56  |
| Carotid Surgery                          | 28%         | 30%          | P=0.82  |
| Infra-inguinal Surgery                   | 68%         | 61%          | P=0.45  |
| Length of Stay                           | 3.5±2.9     | 3.3±3.7      | P=0.75  |
| C-reactive protein @ 24 hours (mg%)*     | 18.2 (9.6-45.1) | 23.0 (12.4-40.0) | P=0.46  |
| NT Pro-BNP @ 24 hours (pg/ml)*           | 609 (308-1323) | 448 (85-361) | P=0.25  |
| Troponin I @ 24 hours (µg/ml)            | 0.010±0.018 | 0.067±0.078 | P=0.22  |
Discussion

This is a secondary analysis of our initial randomized controlled trial, which has shown that preoperative administration of CoQ$_{10}$ reduces post-operative NT Pro-BNP levels but not C-reactive protein levels (13). Prior studies have advocated use of BNP as a preoperative clinical risk variable (11, 12) and may justify larger studies to test whether lowering BNP levels improves long-term outcomes. The principal finding of the present study is that baseline CRP levels were a strong predictor of readmission to the hospital within 1-year of hospital discharge. Along with diabetes and active smoking, modifying CRP preoperatively with additional interventions might be reasonable goals, for reducing readmissions following elective vascular surgery.

Readmission rates have been deemed an important measure of quality of care. As part of the Affordable Care Act (ACA) from 2010, the center for Medicare and Medicaid Services (CMS) has developed new policies to reduce readmissions to the hospital. Among Medicare Beneficiaries undergoing vascular surgery, 24% were readmitted within 30 days of hospital discharge and was second only to congestive heart failure, as the most common DRG-related cause of readmission (1). We have looked at ways of reducing readmissions among patients who were discharged from the hospital following a myocardial infarction, and have found that some patients might be better screened in the emergency room (21). Readmissions following vascular surgery are often unplanned (2, 3) with identifiable risks at the time of discharge that include age, chronic illnesses, socio-economic factors and chronic limb ischemia (4-8). Although our cohort of patients undergoing elective vascular surgery was a heterogeneous group, all of the patients were scheduled for elective procedures and for that reason, had stable, non-urgent presentations. In fact, the patients were screened within 1 week of the procedure and after giving consent, were provided with the tablets to take for 3 days prior to surgery. The study protocol was focused on characterization of biomarkers prior to and following surgery and our goal was to test whether preoperative administration of ubiquinol could lower the biomarkers following surgery. NT Pro-BNP levels are an important predictor of perioperative risk in patients undergoing non-cardiac surgery and our study not only supports that contention but shows that BNP levels can be lowered with preoperative administration of CoQ$_{10}$ (13). CRP levels however were not different between the treatment and placebo groups, suggesting that additional interventions might be needed to reduce either oxidant stress or non-specific inflammatory marker elevations following surgery.
Among patients presenting with an acute coronary syndrome and undergoing coronary interventions, pre-procedural C-reactive protein is an independent predictor of readmission to the hospital within 6 months of hospital discharge (10, 22). Clearly, targeting inflammation as a way of improving outcomes in patients with cardiovascular diseases is an important initiative (14). In fact, among patients with a recent myocardial infarction and an elevated high sensitivity C-reactive protein (≥ 2.0 mg%), the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial demonstrated that inhibition of interleukin-1β (IL-1β) reduces the composite of adverse vascular events and mortality (23). Canakinumab is a monoclonal antibody that inhibits the release of C-reactive protein, by blocking IL-1β and the subsequent release of IL-6 (24). Among consecutive hospitalized patients, those with an elevated C-reactive protein identifies increased risk of readmission to the hospital, when normalized to albumin ratios and blood glucose levels (16). This underscores the important relationship between nutritional status, and the metabolic syndrome, that may complicate the early postoperative recovery period with risks of subsequent infections. In support of our observations, an elevated CRP level at baseline prior to cardiac surgery is an important predictor of adverse outcomes following hospital discharge (25-27) and among patients undergoing vascular surgery, predicts early graft failure (28). Among large groups of patients with known vascular disease, there is growing awareness that an elevated CRP level is an important identifier of recurrent vascular events, and potentially modifiable with newer, novel anti-inflammatory regimens (29-32).

In summary, an elevated baseline CRP level in patients undergoing elective vascular surgery is an important biomarker for identifying those patients at increased risk of readmission to the hospital. Additional significant clinical risks for readmission using multivariate regression include diabetes mellitus and active smoking. We have shown that a short period of CoQ_{10} administration reduces BNP levels, which are an important predictor of perioperative adverse events. Future studies should address whether a longer period of administration of CoQ_{10} prior to high-risk operations, might inhibit C-reactive protein release as well, and potentially reduce risk of readmissions to the hospital following elective vascular surgery.

**Abbreviations**

BNP (B-type natriuretic peptide)

NT Pro-BNP (N-terminal-pro hormone BNP)

DRG (Diagnosis Related Group)

CRP (C-reactive Protein)

CoQ_{10} (Ubiquinone)

VA (Veterans Affairs)
Declarations

Ethics approval and consent to participate - All subjects consented to participate in the study. The study was approved by the local IRB.

Consent for publication - Present

Availability of data and material - Present

Competing interests - None

Funding - None

Authors' contributions - All authors participated in the design, collection, interpretation and expression of the data.

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As shown by the Study Design, patients were screened within 1 week of elective vascular surgery and eligible patients were randomized to receive either CoQ10 or placebo, administered in a double-blind fashion. Biomarkers were obtained prior to and following elective vascular surgery and clinical events collected up to one year following discharge.
Figure 2

Diagnoses at the time of readmission and time frame following discharge from the initial surgical procedure are shown, with infection being the more common diagnosis within the first 30 days.

Figure 3

- Diabetes Mellitus: HR-3.60 (1.46-8.91)
- Active Smoker: HR-3.55 (1.43-8.78)
- CRP ≥ 2mg%: HR-1.35 (1.04-1.76)
Independent risk variables for readmission to the hospital are shown, along with hazard ratio and 95% confidence intervals. The C-index for the prediction of readmission to the hospital based on the presence of all variables was 0.73.