PROGNOSTIC VALUE OF PERIOPERATIVE CARDIAC TROPONIN I COMPARED TO CREATINE KINASE-MB FRACTION AND TO HIGH SENSITIVITY C-REACTIVE PROTEIN IN VASCULAR SURGERY

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I-Introduction

Non-cardiac surgical interventions offer the ability to cure diseases and improve patient's quality of life. The number of patients undergoing non-cardiac surgery is growing. Worldwide estimates suggest that 200 million adults annually undergo major non-cardiac surgery (*Ledy et al., 2011*).

The incidence of perioperative myocardial infarction (MI) in major vascular surgery is 4-5% and cardiovascular complications comprise a major cause of morbidity and mortality affecting both short-term and long-term prognosis (*Flu et al., 2010*).

The pathophysiology of perioperative cardiac events is due to coronary plaque ruptures with subsequent thrombus formation, or prolonged myocardial ischemia. The high frequency of perioperative cardiac complications reflect the high prevalence of underlying coronary artery disease, present in severe form in 28% of patients undergoing major vascular surgery (*McFalls et al., 2008*).

Perioperative myocardial damage is difficult to diagnose due to its silent nature; however, in recent studies perioperative myocardial damage, defined as postoperative Troponin elevation, has been related to adverse short-, mid-and long-term cardiac morbidity and mortality (*Barbagallo et al., 2006*).

Currently, biochemical markers including cardiac Troponin I (cTnI), Creatine Kinase-muscle and brain fraction (CK-MB), high-sensitivity C-reactive protein (hs-CRP), and N-terminal pro-B-type natriuretic peptide, are increasingly used for cardiac risk stratification (*Goei et al., 2009*).

Cardiac biomarkers are substances that get released into the blood when the heart is damaged. Cardiac biomarkers can be detected in blood by a specialized immunoassay and they are very useful in the diagnosis of chest pain patients with non-diagnostic electrocardiogram. They are also used as prognostic indicators of myocardial infarction and to identify patients having an increased risk of cardiac events (*Singh et al., 2011*).

The CTnI is a contractile protein that regulates the interactions of actin and myosin in cardiac muscle and it is highly sensitive and specific marker of myocardial necrosis. Creatine kinase(CK) is an enzyme responsible for transferring a phosphate group from ATP to creatine. Total CK is not cardiac specific but CK-MB is a sensitive as well as specific marker for myocardial infarction. C-reactive protein(CRP), in particular when measured using high-sensitivity assays (hs-CRP), has been suggested as a potentially useful prognostic marker for cardiovascular diseases and it is considered to be directly involved in coronary plaque atherogenesis (*Singh et al., 2011*).

Recent studies suggest that measurement of cTnI or CK-MB after surgery may independently predict a patient's intermediate(less than 12 months), or long-term(more than 12 months) risk of death and major cardiovascular events (*Oscarsson et al., 2004*).

Based on these findings, some investigators have advocated monitoring perioperative cTnI measurements in patients undergoing non cardiac surgery to identify patients at risk (*Kim et al., 2002*).

II-Aim of the work

The aim of the present study is to evaluate comparatively the prognostic value of cTnI, CK-MB, and hs-CRP for short-term (less than 1 month) cardiovascular mortality and morbidity after non-cardiac vascular surgery.

III-Review of Literature

IV-Patients and Methods

A total of 80 consecutive patients of both sexes, aged 50 years old and above, undergoing elective vascular surgeries including peripheral vascular surgery, peripheral embolectomy surgery, aneurysm repair surgery, carotid surgery, and infrarenal aortic surgery, will be enrolled in the study.

After Research Ethics Committee (REC) protocol approval, all patients eligible for the study will provide a written informed consent. The study will be done at Vascular Department of Ain Shams University Hospitals and patients will be prospectively followed-up over a period of one month.

Exclusion criteria:

1-Age below 50 years old.
2-Emergency surgery.
3-Reoperation within 30 days after a previous vascular procedure.
4-Preoperative renal impairment detected by serum creatinine level above 2 mg/dl.
5-Preoperative serum elevation of one of the cardiac markers to be studied.

Methods:

1-Data collection at inclusion:

-Age, gender, date of admission, type of surgery.
-The method of communication for the postoperative outpatient follow-up.
-A complete history taking and physical examination with records of any medical problems such as chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), diabetes mellitus, hypertension, and smoking. All medical problems will be diagnosed by a specialized internist.
-All patients will be subjected to routine preoperative investigations in the form of complete blood picture, complete liver and kidney profile analysis, fasting blood sugar, a preoperative electrocardiogram (ECG), and a preoperative echocardiography. ECG will be repeated on days 1 and 3 of the patient's hospital stay.
-All patients will continue to receive their prescribed medications and will resume them as soon as possible after surgery.
-All patients will be treated by the same surgical and anesthesiology team and type of anesthesia will be recorded in each surgery.

2-Biochemical assay:

Serial blood samples will be drawn from all 80 patients to measure serum cTnI, CK-MB, and hs-CRP preoperatively and 24 hours postoperatively, and whenever clinically indicated in any postoperative cardiovascular event. Serum cTnI, CK-MB, and hs-CRP will be measured

quantitavely using immunoenzymometric assay (Type 3) by Monobind Inc.(Lake forest,CA,USA).

In the analysis of the endpoints, only events occurring within one month of operation will be taken into consideration for the calculation of the predictive value of these biomarkers.

The primary endpoint is detecting and comparing **acute myocardial infarction** , **unstable angina**, **ischemic stroke**, and **death from cardiac causes** including acute MI, cardiac arrhythmia, or congestive heart failure.

The diagnosis of myocardial infarction(MI) will be based on elevated serum cardiac biomarkers with new ECG changes suggestive of ischemia or MI. Unstable angina will be defined as severe chest pain lasting for at least 30 minutes, not responding to treatment, and without CK-MB serum elevation. The diagnosis of ischemic stroke will be made clinically and confirmed with imaging studies.

Patients will be followed-up for the first month after surgery. Any of these events occurring within this period will be recorded for the calculation of the predictive value of each cardiac biomarker.

V-Results:

Any cardiovascular endpoint will be recorded and all cardiac biomarkers associating these events will be compared as regard prediction and sensitivity and will be statistically analyzed using SPSSwin statistical package version 16. Numerical data will be expressed as mean ± standard deviation or median and range as appropriate. Qualitative data will be expressed as frequency and percentage. Chi-square test will be used to examine the relation between the qualitative variables. For quantitative data, comparison between two groups will be done using parametric or non-parametric t-test. Comparison between 3 groups will be done using parametric or non-parametric ANOVA test. P-value of 0.05 or less will be considered significant.

VI-Discussion
VII-Summary
VIII-Conclusion
IX-References
X-Arabic summary

References

1-M Ledy, DH Ansdell, M Phandary, et al. (2011).
Prognostic value of troponin and creatine kinase-muscle and brain isoenzyme measurement after non-cardiac surgery. N. Physiology; 114:732-3.

2-WJ Flu , O Schouten , JPVan Kuijk, and D Poldermans (2010).
Perioperative cardiac damage in vascular surgery patients.Eur J Vasc Endovasc Surg;40:1-8.

3-EO McFalls, HB Ward, TE Moritz, FS Apple, S Goldman, G Pierpont, GC Larsen, B Hattler, K Shunk, F Littooy, S Santilli, J Rapp , L Thottapuratho, W Krupski, DJ Reda, and WG Henderson (2008).
Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. Eur Heart J;29(3):394-401.

4-M Barbagallo, A Casati, E Spadini , G Bertolizio, L Kepgang, T Tecchio, P Salcuni, A Rolli, E Orlandelli, E Rossini, and G Fanelli (2006).
Early increases in cardiac troponin levels after major vascular surgery is associated with an increased frequency of delayed cardiac complications. J Clin Anesth;18(4):280-5.

5-D Goei, WJ Flu, SE Hoeks , W Galal, M Dunkelgrun, E Boersma, et al. (2009). The inter-relationship between preoperative anemia and N terminal pro-B-type natriuretic peptide: the effect on predicting postoperative cardiac
outcome in vascular surgery patients. Anesth Analg;109:1403-1408.

6-TP Singh, AK Nigam, AK Gupta, and B Singh (2011).
Cardiac Biomarkers: When to test?-Physician Perspective. JIACM;12(2):117-21.

7-A Oscarsson, C Eintrei, S Anskar, O Engdahl, L Fagerstrom, P Blomqvist, M Fredriksson, and E Swahn (2004).
Troponin T values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. Acta anaesthesiol Scand;48:1071-9.

8-LJ Kim, EA Martinez, N Faraday, T Dorman, LA Fleisher, BA Perler, GM Williams, D Chan, and PJ Pronovost (2002).
Cardiac troponin I predicts short-term mortality in vascular surgery patients.Circulation;106:2366-71.

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LIST OF ABBREVIATIONS

AAA	:	Abdominal aortic aneurysm
ACEs	:	Adverse cardiac events
AS	:	Aortic stenosis
ADP	:	Adenosine di phosphate
APNs	:	Advanced practice nurses
ACC	:	American college of cardiology
AHA	:	American heart Association
AT	:	Anaerobic threshold
ACE	:	Angiotensin Converting Enzyme
ARBs	:	Angiotensin II receptor blockers
AST	:	Aspartate Transaminase
BP	:	Blood Pressure
CHF	:	Congestive heart failure
CAD	:	Coronary artery disease
CPET	:	Cardiopulmonary exercise testing
CRI	:	Cardiac Risk index
CVA	:	Cerebrovascular accident
CK	:	Creatine Kinase
cTnT	:	Cardiac Troponin T
cTnI	:	Cardiac Troponin I
cTnC	:	Cardiac Troponin C
CRP	:	c reactive protein
CV	:	Coefficient of variation
DRC	:	Dose response curve
DASI	:	Duke activity status index
ESC	:	European society of cardiology
ECG	:	Electrocardiogram
hs-CRP	:	High sensitivity c reactive protein
hFABP	:	Heart fatty acid binding protein
HRS	:	High risk surgery
ISWT	:	Incremental shuttle walk test
IRS	:	Intermediate risk surgery
LRS	:	Low risk surgery
LDH	:	Lactate dehydrogenase
MIs	:	Myocardialinfractions

MET	:	Metabolic equivalent of the task
MCRI	:	Modified cardiac risk index
NCS	:	Non cardiac surgery
PCCs	:	Postoperative cardiac complications
PMI	:	Perioperative myocardial infarction
PAF	:	Platelet activating factor
PRRs	:	Patient related risks

PERIOPERATIVE CARDIAC EVENTS

More than 230 million major surgeries are performed annually worldwide ***(Weiser et al., 2008),*** and this number grows continuously. The 30-day mortality associated with moderate- to high-risk non-cardiac surgery in large cohorts and population-based studies exceeds 2% and surpasses 5% in patients at high cardiac risk ***(Lindenauer et al., 2005; Wu et al., 2007).*** Postoperative cardiac complications (PCCs) constitute the most common cause of postoperative morbidity and mortality, having considerable impact on the length and cost of hospitalization ***(Mackey et al., 2006)***.

Perioperative cardiac complications in vascular surgery:

Cardiovascular complications were highest in vascular surgery patients who had an incidence of 6.2% for cardiac events. The high frequency of perioperative cardiac complications reflects the high prevalence of underlying coronary artery disease, present in severe form in 28% of patients undergoing infrainguinal arterial reconstruction and 36% of patients undergoing abdominal aortic aneurysm repair ***(Mangano et al., 1995).***

Furthermore, it was already known that Myocardial Infarctions (MIs) occur unnoticed out with the operative setting. A review of eight large cohort studies with samples over 100 evaluating the frequency of unrecognized MIs revealed that of 65.000 people, 3.237 MIs occurred, of

which 945 were not detected at the time of the event ***(Devereaux et al., 2005).***

Magnitude of the problem:

Most of the data regarding the incidence of perioperative cardiac events was collected in the 1980's and 1990's, before cardiac specific biomarkers became available. Major adverse cardiac events (MACE's) were found to occur in 2% of relatively unselected patients (not limited to patients with a known risk for coronary artery disease) undergoing noncardiac surgery (NCS) to up to 34% in high risk patients ***(Lee et al. 1999)***.

Similarly ***Poldermans and coworkers (1999)*** reported a 34% incidence of ACE's in high risk patients. In spite of advancement in perioperative medicine this similar incidence of adverse postoperative cardiac events, over the years, can be attributed to an increasing number of elderly patients presenting for more invasive diagnostic and complex surgical procedures ***(Vernick et al., 2008)***.

As the prevalence of chronic disease conditions including cardiovascular disease, cerebrovascular disease and diabetes increases with age and 25% of surgical procedures performed in this elderly population come under the category of high to intermediate risk, there will be a disproportionate increase in the number of patients at risk for perioperative ACE's ***(Schoenborn and Heyman, 2009)***.

In a cohort of 3790 patients undergoing NCS ***Fleischmann and colleagues (2003)*** found that cardiac complications increased mean length of hospital stay by 11 days. Patients experiencing a MI or cardiac arrest after NCS are known to have increased mortality in hospital and following discharge ***(Kumar et al., 2001; Sprung et al., 2003)***. In total, perioperative ACE's and their consequent outcomes cause an astounding increase in health care costs ***(Parent and Rinfret , 2008)***.

General anesthesia and surgery contribute to major cardiac complications because of their propensity for decreased myocardial contractility, increased myocardial irritability, and decreased central venous and arterial pressures from volume shifts and blood loss ***(Jassal et al., 2011)***.

Induction of general anesthesia may lead to a 20-30% reduction in blood pressure (BP) and a 15% decrease in cardiac output, whereas endotracheal intubation, catecholamine excess, and vasospam may significantly raise BP; all of these are known to have negative influence on cardiovascular physiology. Major PCCs include cardiac arrhythmias, congestive heart failure (CHF), acute MI, and cardiac death ***(Fleisher et al., 2007; Jassal et al., 2011)***.

Cardiac Mortality

Underlying cardiac disease and perioperative complications contribute to the majority of postoperative cardiac mortality, which has