Timing of coronary artery bypass surgery in patients with non-ST-segment elevation myocardial infarction and postoperative outcomes

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Abstract

Introduction: The aim of the study was to assess whether a cardiac troponin T (cTnT) level 1 ng/ml or below threshold is safe and to evaluate mid-term follow-up results in stable patients with non-ST-segment elevation after acute myocardial infarction.

Material and methods: Among cTnT positive patients who presented to the emergency unit with chest pain and received coronary angiography, 100 patients who underwent isolated coronary artery bypass grafting (CABG) constituted the study group (group 1). The same number of patients (n = 100) who were cTnT negative and underwent an isolated CABG operation under elective conditions were selected as the control group (group 2).

Results: Among preoperative criteria, group 1 had significantly higher smoking rates (74% vs. 41%, p = 0.0001), and significantly lower ejection fraction values (47.1 ±8.25, 54.69 ±8.73, p = 0.0001). There were no significant differences between the groups with respect to operative parameters. Postoperative follow-up periods were significantly longer in group 1 (23.25 ±14 vs. 17.55 ±7.95 months, p = 0.001). Average waiting time for cTnT to drop below the 1 ng/ml threshold value was 5.73 ±2.95 (1–12) days. Intra-aortic balloon pump use in Groups 1 and 2 was 3% and 1%, respectively. There were no hospital mortalities in either group. Mortality rates at mid term were 6% in both groups.

Conclusions: This study compared two groups positive and negative for preoperative cTnT. The findings show that it is safe to wait until cTnT levels decrease to the 1 ng/ml threshold value in cTnT positive patients having a stable course. This waiting period is not very long, which is significant with respect to potential complications.

Key words: myocardial infarction, non-ST-segment elevation, coronary artery bypass grafting, timing, troponin-T.

Introduction

It has been clearly shown in numerous studies that emergency coronary artery bypass grafting (CABG) after acute coronary syndrome (ACS)

carries high morbidity and mortality rates. The management strategy is clear in unstable patients who have indications for emergency surgery; however, the timing of surgery in stable ST-segment-elevation myocardial infarction (STEMI) and non-ST-segment-elevation myocardial infarction (NSTEMI) patients remains controversial [1]. The limited number of clinical studies on this issue have reported that surgery during the early period may increase morbidity and mortality. However, depending on different studies, the definition of the early period varies between the first 6 h to 1 month after hospitalization. It is possibly due to this uncertainty that some studies have found CABG in the early phase to be related to increased morbidity and mortality, whereas others did not find such an increased risk [2–8].

Cardiac troponins are highly sensitive and specific laboratory tests which indicate myocardial injury. Diagnosing patients with ACS and determining their treatment alternatives provide valuable information on the prognosis of these patients [9, 10]. There are numerous studies which have shown an association between high preoperative and postoperative troponin levels associated with increased morbidity and mortality rates in patients undergoing CABG [11–14]. This raises the possibility that cardiac troponin levels may be used as a marker for the timing of CABG operations. Thielmann *et al.* [13] found that the subgroup of patients with NSTEMI with troponin I values above 1.5 ng/ml had twice the mortality than those below this level, and the CABG operation could be performed with acceptable risks in patients with troponin I levels under 1.5 ng/ml. For the last 5 years at our institution our practice has been to wait for the cardiac troponin T (cTnT) to drop below 1 ng/ml and perform CABG once the acute phase is over.

In this study, we aimed to investigate the safety of this threshold value and discuss our mid-term results in the light of the current literature.

Material and methods

Patients who presented to the emergency department of our institution between January 2008 and January 2013 were reviewed. Patients were divided into two groups: group 1 (n = 100 patients) comprising patients with positive cTnT levels who underwent the CABG procedure; and group 2 comprising the same number of patients, randomly chosen, with negative cTnT levels who underwent the CABG procedure during the same period. Randomization of the patients in group 2 was arranged by the free use web-based system (http://www.tufts.edu/~gdallal/PLAN.HTM). One hundred patients could be randomized out of 228 patients and remaining patients operated during the same period of time were not taken into account. None of the patients in group 2 had previous STEMI or NSTEMI in their past medical history. Patients who had continuous chest pain while still on medical treatment, were hemodynamically unstable, had life-threatening severe arrhythmias, had post-MI mechanical complications or left main coronary artery lesion of 50% or above, had primary percutaneous intervention (PCI) during coronary angiography, or had a history of a prior CABG operation were excluded from the study. Patients operated off-pump were also excluded for randomization purposes. The patients in group 1 were not discharged from the hospital until their surgery and received anticoagulant treatment with low molecular weight heparin. Troponin levels were assessed daily, and the patients were operated when the cTnT level dropped below 1 ng/ml. Troponin level measurements were made by the electrochemiluminescence method using a Troponin T hs kit (Roche Diagnostics GmbH, Mannheim, Germany).

Surgical procedure

All the patients were operated through full median sternotomy. The grafts were prepared after opening the sternum. The ascending aorta and two-stage right atrium cannulations were performed. Systemic heparinization with 300 U/kg heparin was made, and cardiopulmonary bypass was initiated when activated clotting time (ACT) reached > 400 s. Non-pulsatile perfusion, coated tubing set and membrane oxygenators were used with moderate hypothermia (32–34°C). Antegrade or optional retrograde cold blood cardioplegia was applied for myocardial protection.

Definitions

The NSTEMI is defined as transient ST-segment depression ≥ 1 mm or T wave inversion in 2 or more precordial leads in a patient with chest pain, dyspnea, or lethargy accompanied by elevated troponin and/or creatine kinase-myocardial band (CK-MB).

The presence of diabetes, hypertension, and smoking were determined from the patient histories. Cholesterol levels above 200 mg/ml were accepted as hyperlipidemia, body mass index over 30 kg/m^2 was accepted as obesity, forced expiratory volume exhaled at the end of 1 s (FEV_1)/forced vital capacity (FVC) < 50% was accepted as chronic obstructive pulmonary disease (COPD), and creatinine levels above 0.2 µmol/l were accepted as renal disease. The presence of a 50% or greater stenosis of the carotid arteries on preoperative routine carotid Doppler ultrasonography or other established peripheral artery diseases were accepted as criteria for peripheral vascular disease. In the definition of coronary ar-

tery disease; '0' was used for left main coronary disease (< 50% stenosis), '1', '2' and '3' for single-, two- and three-vessel disease, respectively. Use of adrenaline, dobutamine, dopamine and noradrenaline for inotropic support was recorded numerically from 1 to 4.

Parameters

Both groups were compared with respect to preoperative parameters including demographic data (age, sex), risk factors (diabetes mellitus, hypertension, hyperlipidemia, obesity, smoking), comorbidities (COPD, peripheral vascular disease, renal disease), the extent of coronary artery disease, left ventricle ejection fraction (EF), and EuroSCORE; operative parameters including cross clamp time and perfusion time, number of grafts, and use of the left internal mammary artery (LIMA); and postoperative parameters including duration of ventilatory support, length of stay in the intensive care unit and hospital, requirement for blood and blood product transfusion, revision, inotropic agent use due to low cardiac output, and follow-up period findings. In group I, peak cTnT levels and levels at the onset of surgery, time waited before cTnT dropped to 1 ng/ml or below, and problems encountered during follow-up were recorded. The patients were called for follow-up at the postoperative 1st week, 3rd and 6th weeks, 6th month and every 6 months thereafter. Patients who did not come to the control visit were contacted by telephone and final conditions were recorded.

Statistical analysis

Statistical evaluation was performed with the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) program. Evaluation of the data was made with descriptive statistical methods (mean, standard deviation), the two groups were compared with independent *t* test, and the qualitative data were compared with the χ^2 test. The results were considered significant for $p < 0.05$.

Results

Analysis of preoperative basic characteristics showed that the male sex was predominant in both groups (82% in group 1, and 72% in group 2). There were no statistically significant differences between the groups with respect to age and sex. Analysis of risk factors showed no significant difference except for smoking. Smoking was significantly higher in group 1 compared to group 2 (74% and 41%, respectively; $p = 0.0001$). The differences between comorbidity, extent of coronary artery disease, and EuroSCORE values were not significant. Ejection fraction values were significantly lower in group 1 compared to group 2 (47.1 ±8.25, 54.69 ±8.73; $p = 0.0001$) (Table I). Comparison of operative data showed no significant differences in cross clamp and perfusion times, number of grafts, and use of LIMA (Table I). Evaluation of postoperative values did not show significant differences in duration of ventilatory support, length of stay in the intensive care unit or the hospital, blood and blood product transfusion requirement, revision and use of cardiac inotropic agents. Follow-up periods were significantly longer in group 1 (23.3 ±14 months and 17.6 ±8 months; $p = 0.001$) (Table I). In group 1, the highest cTnT level prior to surgery was 3.2 ±1.8 ng/dl (11.95–1.13), and cTnT level on the day of surgery was 0.6 ±0.3 ng/dl (1.00–0.01). The average time elapsed for the cTnT levels to drop below the 1 ng/ml threshold level was 5.7 ±2.95 (1–12) days. Three patients in group 1 and 1 patient in group 2 required intra-aortic balloon pump (IABP) support. There were no hospital mortalities in either group. Complications seen within the follow-up period were found to be 10% and 8% for myocardial infarction and unstable angina, 12% and 14% for control angiography, 3% and 2% for percutaneous coronary intervention, 4% and 3% for cardiac mortality (Figure 1), and 2% and 3% for noncardiac mortality, in group 1 and 2, respectively. The survival was calculated to be 94% for both groups (Figure 1, Table II).

Discussion

The timing of surgical revascularization after acute myocardial infarction (AMI) is still controversial. Emergency CABG is recommended in patients who have undergone failed or complicated PCI, have signs of ischemia despite medical treatment, complications of AMI, life-threatening arrhythmias and/or hemodynamic instability. Early revascularization may prevent further worsening of the ventricular functions by limiting the progression of the infarct area. It has a positive contribution to ventricular remodeling as well. On the other hand, hemorrhagic complications due to reperfusion injury may widen the infarct area, increase scar tissue and affect the recovery process negatively. Severe ventricular arrhythmias may be encountered following reperfusion. Collateral blood is significantly variable from one patient to another, and affected negatively by hypotension, arrhythmias, and increased left ventricular end diastolic pressure during AMI. Therefore prevention of these arrhythmias and hemodynamic control carry vital significance. The control of symptoms and maintenance with aggressive medical treatment is suggested as a priority [1].

In a series of 4676 patients operated in the early period after AMI, Weiss *et al.* found greater

Table I. Pre-, intra-, post-operative characteristics of the enrolled patient population

Preoperative characteristics of the patients in the groups					
Demographics[1]	**Group 1 (*n* = 100)**	**Group 2 (*n* = 100)**	***t***	**χ^2**	***P*-value**
Age [years]	58.3 ±11.6	61.0 ±8.3	–1.92		0.057
Female gender	18%	28%		2.28	0.130
Cardiovascular risk factors:					
Diabetes mellitus	38%	45%		1.01	0.315
Hypertension	63%	80%		2.82	0.082
Hyperlipidemia	46%	45%		0.02	0.887
Obesity[2]	25%	26%		0.03	0.871
Smoking history	74%	41%		22.28	0.0001
Comorbidities:					
COPD	10%	14%		0.76	0.384
PVD	14%	15%		0.04	0.841
Renal disease[3]	13%	12%		0.05	0.831
Extent of CAD:					
Left main stem disease*	16%	10%			
One vessel disease	7%	7%			
Two vessel disease	16%	26%			
Three vessel disease	61%	57%		3.9	0.272
LVEF	47.1 ±8.3	54.7 ±8.7	–6.32		0.0001
EuroSCORE	2.2 ±1.9	2.1 ±1.8	0.15		0.879
Operative characteristics:					
ACC time [min]	43.7 ±20.6	45.1 ±13.0	–0.58		0.560
CPB time [min]	73.6 ±33.5	72.8 ±19.0	0.21		0.834
Grafts per patient	3.2 ±1.1	3.1 ±0.9	0.71		0.476
IMA grafts	99%	97%	1.02		0.312
Postoperative characteristics:					
Ventilation time [h]	9.9 ±7.7	9.4 ±3.3	0.70		0.488
ICU stay [day]	1.8 ±1.2	1.8 ±0.8	0.35		0.724
Hospital stay [day]	6.1 ±2.0	5.67 ±1.0	1.74		0.083
Blood transfusion [U]	1.6 ±0.9	1.5 ±1.0	0.14		0.886
Revision rate	3%	2%	0.21		0.651
IABP support, *n*	3	1			0.064
Inotrope use:					
No inotrope	37%	49%		2.93	
One inotrope	50%	35%		4.60	
Two inotropes	11%	16%		1.07	
Three inotropes	2%	0%		2.02	
Following time [months]	23.3 ±14	17.6 ±8.0	3.54		0.001

*CAD – coronary artery disease, COPD – chronic obstructive pulmonary disease, PVD – peripheral vascular disease, LVEF – left ventricular ejection fraction, ACC – aortic cross-clamp, ACC – aortic cross-clamp, CPB – cardiopulmonary bypass, IMA – internal mammary artery, IABP – intra-aortic balloon pump support; [1]Continuous data are presented as mean ± standard deviation, [2]body mass index > 30 kg/m², [3]serum creatinine > 0.2 mmol/l, *< 50% stenosis.*

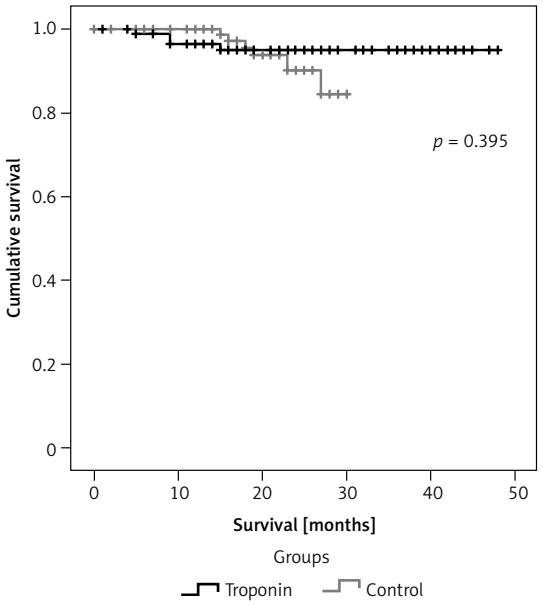

Figure 1. Kaplan-Meier curve for mid-term mortality

mortality in the group of patients operated within the first 2 days compared to those operated on the 3rd day or later. The authors suggested to wait at least 3 days before CABG, except for emergency conditions [15]. Thielmann *et at.* found an 8.7% hospital mortality rate in patients with AMI with ST elevation (n = 138). In the same study, analysis of symptom onset, timing of surgery and hospital mortality rates showed that the highest mortality rates were between 7 h and 23 h (23.8%), and the lowest were between 8 and 14 days (2.4%). The hospital mortality rates in another study were found to between 3.0 and 6.6% in AMI patients with high cTnI levels and non-ST segment elevation [13]. In a similar study, Cresswell *et al.* [6] observed that the greatest operative mortality after AMI was seen in 11 patients (9.1%) operated within the first 6 h. In the same study, the operative mortality decreased to 2.9% in 1023 patients operated 6 weeks later, and the total mortality in 3942 patients was 3.5%. The mortality of 1646 non-AMI patients who underwent elective surgery was 2.1% [6]. In summary, the hospital mortality of AMI patients who require surgical revascularization approaches the rates of an elective group of patients if they can be kept stable during the acute phase.

When patients with NSTEMI are examined separately, it is seen that the difference in mortalities between the early and late revascularization groups is smaller, or there is no difference according to some studies. In a retrospective study including 283 NSTEMI patients, Braxton *et al.* found no difference between the mortality rates in patients undergoing CABG before or after 48 h, and concluded that these patients could be operated

Table II. Complications and mortality in follow-up period

Characteristics	Group 1	Group 2
MI, unstable angina	10%	8%
Control angiography	12%	14%
PCI	3%	2%
Cardiac death	4%	3%
Non-cardiac death	2%	3%
Survival	94%	94%

MI – myocardial infarction, PCI – percutaneous coronary intervention.

at any time after MI with mortality rates similar to those of control patients who did not sustain MI (3.5% vs. 2.4%, p not significant) [2]. Gertler *et al.* [3] investigated the same question, and found that there was no difference in mortalities when patients were operated within the first 12 days or afterwards. Parikh *et al.* [4] found similar mortality rates in 2647 NSTEMI patients who underwent CABG within the first 48 h after admission to the hospital or later. Deyell *et al.* studied a cohort of 1454 patients. Patients who underwent CABG during the early phase between 2 and 7 days after MI had increased mortality compared to those operated during the moderate (8–14 days) and late (15–60 days) phases [5]. Due to these inconsistent results of the studies, stable patients with NSTEMI often wait for weeks before bypass surgery, which results in unnecessary consumption of resources. Also, stable patients who are offered to undergo surgery after coronary angiography carry the risk of sustaining a new MI at home when they are discharged from the hospital. The most logical approach appears to be operating on these patients after waiting for a reasonable time and without discharging them. However, what should be the reasonable time? In most studies, the time that elapsed from hospital admission to the operation is used as a threshold value. In these studies, the definition of post-MI early revascularization ranges between 6 h and 1 month, thereby making it difficult to evaluate study results. Inability to make an objective assessment of the time of MI in patients with NSTEMI causes another problem in the evaluation of studies.

The roles of cardiac troponins in predicting the preoperative and postoperative mortality and morbidity have been demonstrated in various studies [9–11]. Filizcan *et al.* [14] showed that cardiac troponin levels were one of the predictive factors for hospital mortality in AMI patients with ST-segment elevation. Paparella *et al.* [16] similarly showed that cTnI levels before surgery played a role in the increase of myocardial injury after surgery and negatively affected mid-term mortality and morbidity. Therefore, it may be predicted that waiting for

cTnT levels to fall to a certain level may decrease postoperative morbidity and mortality. In patients with NSTEMI, waiting for the cTnT to decrease to a quantitative level (1 ng/ml) eliminates most of the uncertainties stated above. The mortality of isolated CABG is below 1% in most studies. In one series, hospital mortality rates in 2337 patients with low risk and 2272 patients with moderate risk were found to be 0.9% and 1.7%, respectively [17]. In our study, the absence of hospital mortality in both groups is similar to other studies [18–20] with respect to the troponin negative group 2, and also shows that it is more successful than other series with respect to troponin positive group 1 patients. During the follow-up period the rates for myocardial infarction, unstable angina, angiography for control purposes, percutaneous coronary intervention, cardiac and non-cardiac mortalities were as expected, and 94% survival rates were found to be satisfactory.

In conclusion, the results of the current research indicated the safety of delaying CABG until the cTnT levels fall below the 1 ng/ml threshold in patients with a stable course after AMI. The waiting period is usually not very long, which is important for the prevention of complications that may develop as a consequence of AMI.

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