Prognostic value of troponin I after elective percutaneous coronary intervention

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Abstract

Introduction: The significance of troponin I (Tn-I) elevation after percutaneous coronary intervention (PCI) is the subject of debate. **Objective:** To determine cardiovascular prognosis associated with Tn-I elevation one year after successful elective PCI. **Methods:** Observational, retrospective, longitudinal study. Patients who underwent successful elective PCI were included and divided in two groups: with and without Tn-I elevation, in order to compare the occurrence of major adverse cardiac events (MACE) at 1 year; post-PCI Tn-I was correlated with demographic and angiographic characteristics. **Results:** Tn-I elevation was detected in 32 patients (35.2%). Elevation was more common in patients with multivascular and more complex coronary artery disease, and with peri-PCI complications. MACE incidence at one year was higher in the elevated Tn-I group (25% vs. 3.4%; $p = 0.002$). Independent predictors of MACE were Tn-I 5-fold elevation from normal value (OR: 7.5; 95% CI: 1.25-45; $p = 0.027$) and peri-PCI complications (OR: 7.5; 95% CI: 1.25-45; $p = 0.027$). **Conclusions:** In patients with stable coronary artery disease, Tn-I elevation after successful elective PCI is associated with adverse cardiac events at 1 year, more extensive and complex coronary artery disease and peri-PCI complications.

KEY WORDS: Troponin I. Percutaneous coronary intervention. Major adverse cardiovascular events.

Introduction

Acute coronary syndromes are an important cause of morbidity and mortality in the world.¹ In Mexico, they are the number one cause of death in subjects older than 60 years^{2,3} and their prevalence is expected to increase in next years.⁴ Percutaneous coronary intervention (PCI) has become a widely used therapy that is effective in ischemic heart disease, with nearly 1.7 million procedures performed annually and an immediate success rate > 90 %.⁵ Severe complications are rare;⁶ however, small increases in troponin and creatine phosphokinase MB fraction (CPK-MB) levels are often found after elective coronary angioplasty in patients with a successful procedure.^{7,8} Troponin and CPK-MB elevation after coronary angioplasty has been documented to occur in 5 to 50 % of patients.^{9,10}

Although troponin I (Tn-I) importance and prognostic value in patients with acute coronary syndrome are clear, the prognostic significance of this biomarker elevation after elective percutaneous coronary intervention remains a subject of debate. Previous results on association of its elevation after elective PCI and cardiac events are not clear and ambiguous.¹¹ Studies with magnetic resonance imaging have shown that even small increases in CPK-MB and troponin are associated with new irreversible myocardial damage and that, in addition, there is positive correlation between the magnitude of damage and troponin release extent.^{12,13} This myocardial damage might cause cardiac function deterioration, affecting subsequent prognosis of patients.^{14,15}

The purpose of our study was to determine major adverse cardiac events (MACE) prognostic implication at one year, associated with a Tn-I value increase

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above reference values after successful elective percutaneous coronary intervention.

Method

Patients of either gender, of any age, diagnosed with stable chronic angina, who had undergone elective percutaneous coronary intervention that was considered to be successful between May 14, 2013 and May 14, 2014, were included. Post-procedure myonecrosis biomarker levels were determined, with the sample being divided in two groups for analysis and comparison: patients with and without Tn-I elevation above the reference value. Clinical, demographic and angiographic variables were analyzed, as well as the presence of MACE, at one year of follow-up in both groups in order to compare them with each other. Patients with recent acute coronary syndrome (at less than 7 days) and with incomplete medical records were excluded from the study.

Coronary lesions were assessed during the procedure by means of coronary angiography with multiple orthogonal views. All angioplasties were carried out with standard techniques. Prior to CPI, patients were treated with 150 to 300 mg acetylsalicylic acid, and if the decision was made to place one or several stents, they received a clopidogrel loading dose of 300 to 600 mg prior to implantation. During the CPI, patients were treated with 100 U/kg of intravenous heparin. The decision on radial versus femoral approach, stent placement, use of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors and intra-aortic balloon counterpulsation was left to the discretion of the interventional cardiologist. After the CPI, acetylsalicylic acid use was recommended indefinitely and clopidogrel for 3 to 12 months, depending on the type of implanted stent (medicated versus non-medicated). Angiographic lesions were classified according to American Heart Association/American College of Cardiology (AHA/ACC) criteria. A successful procedure was defined by a coronary artery residual stenosis < 30 %, with a thrombolysis in myocardial infarction (TIMI) grade 3 coronary flow, according to the American Heart Association/American College of Cardiology coronary intervention management guidelines.

Serum cardiac biomarker samples (Tn-I and CPK-MB) were obtained at 6 and 12 hours of the procedure. If the results were abnormal, subsequent samples were taken until peak level was established. Tn-I and CPK-MB serum values were determined by means of chemiluminescent microparticle immunoassay with Architect System 4100® (Abbot Diagnostics), with an

Table 1. Variables associated with post-procedure troponin I increase

Variable	OR	CI	p
Bifurcation PCI	3.33	1.1-9.4	0.020
Elevated CK-MB	7.2	2.7-19.1	< 0.001
Peri-PCI complications	9.7	2.4-38.5	< 0.001
23 to 32-point syntax	4.0	1.3-12.4	0.012

CI=confidence interval, CPK-MB=creatinine phosphokinase MB, OR=odds ratio, PCI=percutaneous coronary intervention.

upper limit of normal (ULN) of 0.40 ng/mL for TN-I and 24 U/L for CPK-MB.

Data were obtained by means of telephone interviews to patients and their families and by means of electronic medical records review. A standardized form was used to document MACEs: death, acute myocardial infarction, new PCI and myocardial revascularization surgery.

Non-categorical variables were expressed with central tendency measures (mean) and dispersion measures (standard deviation), whereas categorical variables were expressed using simple and relative frequency. Tn-I highest post-CPI value was used for analysis. Categorical variables comparisons were made using the chi-square test, whereas non-categorical variables were compared with Mann-Whitney U-test owing to asymmetric distribution of the sample. Univariate analysis was carried out with the chi-square test to assess clinical-demographic, angiographic and procedure characteristics associated with Tn-I elevation. A logistic regression multivariate analysis model was used to determine factors independently related to the incidence of major adverse cardiac events at one year of follow-up. A p-value ≤ 0.05 was considered statistically significant for all analyses. The SPSS statistical program, version 22, was used.

Results

From May 13, 2013 to May 14, 2014, 91 patients met the selection criteria; 32 (35.2 %) had troponin elevation (> 0.40 ng/mL), out of which 20 (62.5 %) had post-PCI CK-MB elevation as well (> 24 U/L); 59 patients (64.8 %) showed no Tn-I elevation. Within the elevated Tn-I group, 14 patients (43.8 %) had troponin levels more than 5 x ULN. Categorical variables associated with post-PCI Tn-I elevation are shown in table 1.

Baseline demographic and clinical variables were similar in both groups, except for hospital length of stay,

Table 2. Clinical-demographic characteristics of patients who underwent successful elective percutaneous coronary intervention

Variable	Mean ± SD						p
	Total patients (n = 91)		Elevated Tn-I (n = 32)		Tn-I no elevada (n = 59)		
Age	60.43 ± 10		61.41±10		59.90 ± 11		0.514
Hospital length of stay	2.68 ± 2.27		3.78 ± 3.5		2.08 ± 0.65		0.011
Tn-I peak	4.187 ± 12.6		11.735 ±19.3		0.0941 ± 0.09		< 0.001
CK-MB peak	38.85 ± 66.3		75.82 ± 101.2		18.80 ± 13.5		< 0.001
	n	%	n	%	n	%	
Male gender	66	72.5	21	65.6	45	76.3	0.277
Diabetes mellitus	47	51.6	16	50.0	31	52.5	0.817
Systemic hypertension	67	73.6	26	81.2	41	69.5	0.224
Dyslipidemia	49	53.8	14	43.8	35	59.3	0.155
Smoking	37	40.7	12	37.5	25	42.4	0.651
Previous AMI	38	41.8	13	40.6	25	42.4	0.872
CCS angina class							
I	6	6.6	3	9.4	3	5.1	0.431
II	59	64.8	21	65.6	38	64.4	0.907
III	19	20.9	5	15.6	14	23.7	0.364
IV	7	7.7	3	9.4	4	6.8	0.657
Ischemia study	83	91.2	31	96.9	52	88.1	0.160
EST	34	41	10	32.3	24	46.2	0.375
MS	36	43.4	17	54.8	19	36.5	0.510
DSE	13	15.7	4	12.5	9	15.3	0.720

AMI=acute myocardial infarction, CCS=Canadian Cardiovascular Society, CPK-MB=creatine phosphokinase MB, DSE=dobutamine stress echocardiogram, EST=exercise stress test, MS=myocardial scintigraphy, Tn-I=troponin I.

which was more prolonged in the elevated Tn-I group (3.7 ± 3.5 versus 2 ± 0.65 days, $p = 0.011$) and Tn-I and CPK-MB peak values (Table 2). The majority of patients (83, 91.2 %) had an ischemia-inducing study prior to the procedure, most of them cardiac scintigraphy (43.4 %).

In the group with Tn-I elevation, angiographic and procedure variables (Table 3) revealed larger extension of coronary disease (number of affected vessels), as well as larger number of treated vessels and use of stents. In this group, more complex coronary disease was recorded, with higher Syntax score and more common coronary stenosis management in bifurcations. More frequency of complications was also found in the elevated Tn-I group (11 [34 %] versus 3 [5.1 %], $p = 0.001$). The most common complication in both groups was secondary branch occlusion in 50 %, followed by coronary dissection in 21.4 %.

Major adverse cardiovascular events at 1 year

During the 12-month follow-up, cardiac adverse events were documented in 10 patients (11 %), 8 in the elevated Tn-I group and 2 in the non-elevated Tn-I

group ($p = 0.002$); MACEs for each group are shown in figure 1. In the elevated Tn-I group, the univariate analysis showed that the MACE-related characteristics that were statistically significant at 12 months were peri-PCI complications ($p \leq 0.001$), use of GP IIb/IIIa ($p = 0.013$), Tn-I elevation $> 5 \times$ ULN ($p \leq 0.001$), elevated CK-MB ($p = 0.007$), CK-MB elevation $> 5 \times$ ULN ($p = 0.012$), Tn-I peak value ($p = 0.05$) and days of hospital stay ($p = 0.002$).

The multivariate analysis showed that the variables that were independently associated with a higher incidence of major cardiovascular adverse events were the presence of peri-PCI complications (OR = 7.5, CI = 1.25-45, $p = 0.027$) and troponin increase $> 5 \times$ ULN (OR = 7.5, CI = 1.25-45, $p = 0.027$).

Discussion

We present the results of a series of consecutive patients who underwent successful elective PCI. Only patients with stable coronary disease were included, since Tn-I is a highly sensitive marker of myocardial

Table 3. Angiographic and procedure characteristics

Variable	Mean ± SD						p
	Total patients (n = 91)		Elevated Tn-I (n = 32)		Tn-I no elevada (n = 59)		
Compromised vessels	1.73 ± 0.87		2.00 ± 0.84		1.58 ± 0.85		0.009
Treated vessels	1.45 ± 0.601		1.66 ± 0.70		1.34 ± 0.51		0.028
Stents placed	1.97 ± 1.15		2.31 ± 1.23		1.78 ± 1.08		0.029
LVEF	51.43 ± 7.7		51.41 ± 8.7		51.44 ± 7.2		0.633
	n	%	n	%	n	%	
Syntax < 22	69	75.8	19	59.4	50	84.7	0.007
Syntax 23-32	16	17.6	10	31.2	6	10.2	0.012
Syntax > 33	6	6.6	3	9.4	3	5.1	0.358
PCI with stent	90	98.9	32	100	58	98.3	0.459
AHA/ACC B2/C PCI lesion	63	69.2	24	75	39	66.1	0.380
Bifurcation PCI	19	20.9	11	34.4	8	13.6	0.020
Multi-vessel PCI	17	18.7	9	28.1	8	13.6	0.089
GP IIB/IIIA inhibitor	9	9.9	5	15.6	4	6.8	0.177
Procedure complications	14	15.4	11	34.4	3	5.1	< 0.001
Dissection	3	21.4	2	18.2	1	33.3	
Secondary branch occlusion	7	50	5	45.5	2	66.7	
Acute thrombosis	1	7.1	1	9.1	0	0	
No reflow	0	0	0	0	0	0	
Perforation	1	7.1	1	9.1	0	0	
Sustained hypotension	1	7.1	1	9.1	0	0	
Vasospasm	1	7.1	1	9.1	0	0	

ACC=American College of Cardiology, AHA=American Heart Association, CPK-MB=creatine phosphokinase, GP=glycoprotein, LVEF=left ventricular ejection fraction, PCI=percutaneous coronary intervention, Tn-I=troponin I.

Figure 1. Cardiovascular adverse events at 12 months of follow-up in the groups with and without troponin I elevation. AMI = acute myocardial infarction, PCI = percutaneous coronary intervention, MRS = myocardial revascularization surgery, Tn-I = troponin I.

damage that has prognostic value in patients admitted to the hospital with acute coronary syndrome.

The frequency of Tn-I elevation in our study was 35.2 %, similar to Cavallini et al.⁹ and Ertan et al.¹⁶ previously reported figures, in studies where 39.4 and 34 % of patients, respectively, showed post-PCI Tn-I levels increase. Other investigations have reported lower figures, such as a 13.2 % prevalence observed by Zhang et al.¹⁰ and others have reported a frequency as high as 44.2 %, as Claudio et al. did.⁵

There are several situations that have been associated with troponin elevation after elective PCI. Factors related to the patient include multi-vessel disease, kidney failure, old age, intervention in de novo lesions, left ventricular ejection fraction decrease, intervention in saphenous vein grafts and in complex lesions. Factors related to the procedure have been reported, including: no-reflow phenomenon, insufflation prolonged time, vessel abrupt closure, sustained chest pain (> 5 minutes), long lesion (> 20 mm), distal embolization, thrombus formation, vessel dissection, hypotension, stent over-expansion and secondary branch occlusion.^{9,11,16-20}

In our study, post-PCI elevation predictors were found to be intervention in bifurcation, elevated CPK-MB above ULN, 23 to 32 Syntax score, longer hospital stay, higher number of compromised and treated vessels, higher number of stents placed and higher statistical association with the development of peri-PCI complications (OR = 97, CI = 2.4-38.5, $p \leq 0.001$). These observations are consistent with previous studies that have implicated peri-PCI complications as the main mechanism responsible for the existence of myonecrosis.⁹

Nienhuis et al. demonstrated that patients with multiple-vessel angioplasty are more likely to have increased troponin levels and to experience cardiovascular events in comparison with patients with single-vessel angioplasty (31.5 versus 18.3 % and 28 versus 19 %, respectively).²¹ In our study, multi-vessel disease was more common in patients with Tn-I elevation (28.1 versus 13.6 %), with the difference not being statistically significant ($p = 0.089$).

CPK and CPK-MB elevation after elective PCI has been associated in previous studies with an increase in the risk of death, acute myocardial infarction and repeated revascularization;²²⁻²⁴ however, other have not shown any relationship between elevation of these cardiac markers and survival.²⁵⁻²⁷

Currently, there is no consensus in the literature regarding the prognostic value of Tn-I concentrations increase after elective PCI. In a study carried out by

Mark et al.,¹⁸ post-elective PCI Tn-I increase was shown to have a strong prognostic implication, whereas Ertan et al.¹⁶ concluded that Tn-I elevation after successful PCI is not associated with late cardiac adverse events. Nienhuis et al.¹¹ conducted a meta-analysis of 20 studies published from 1998 to 2007 that included 15 581 patients. Troponin was found to be elevated in 32.9 %. During a mean follow-up of 16.3 months, an increase in mortality was found that was significantly associated with post-PCI troponin elevation (4.4 versus 3.3 %, $p = 0.001$, OR = 1.35). The combination of death and non-fatal myocardial infarction was also more common in the group with post-PCI Tn-I elevation (8.1 versus 5.2 %, $p < 0.001$, OR = 1.59). The meta-analysis concluded that troponin elevation after elective PCI provides important prognostic information.

In our study, 10 patients (11 %) experienced major adverse cardiovascular events. Ricciarddi et al.,²⁰ during a mean follow-up of 444.6 days, demonstrated that 27 % of patients experienced at least one major cardiac adverse event, which is a higher number in comparison than that observed in our sample. Overall mortality in our sample was low (1.1 %), similar to that reported by Nienhuis et al.¹⁸ (1 %). MACE predominant form was percutaneous coronary re-intervention (8.8 %), which is a similar finding to that in the study by Naghet et al., where after an 18-month follow-up, patients with post-PCI Tn-I elevation had a MACE rate of 25 % (17.7 % owing to re-PCI).²⁸

Pharmacological interventions that have anti-inflammatory and anti-thrombotic effects such as statins and GP IIb/IIIa inhibitors have demonstrated to reduce the incidence and magnitude of angiographic complications and, therefore, of myonecrosis.^{20,29,30} The use of GP IIb/IIIa inhibitors can reduce microembolization by preventing the formation of thrombi before, during and after PCI, and also has been shown to reduce PCI major ischemic complications by 35 to 56 % in a broad spectrum of angiographic clinical and morphologic situations.¹⁶ In our study, GP IIb/IIIa inhibitors were used in 9 patients (9.9 %), and were more frequently used in patients with Tn-I elevation (15.6 versus 6.8%), with the difference not being statistically significant ($p = 0.177$); they were used mainly in patients who experienced angiographic complications, without better or worse prognosis associated with their use being observed.

Study limitations

Since the present study was observational, retrospective and was carried out in a single hospital center, is

subject to important limitations inherent to its nature: limited number of patients and relatively short follow-up period. As in other previous studies, coronary angiography and PCI analyses were not performed in an independent central angiographic laboratory, and the description of those variables that are potentially relevant for prognosis, such as lesion morphology, coronary artery disease extent, procedure result and revascularization degree, were left at the operator's discretion.

Conclusions

According to the results obtained in the present study, we can conclude that, in our setting, Tn-I elevation in patients with stable coronary disease is associated with higher occurrence of major adverse cardiovascular events at one year. Tn-I elevation is more common in patients more extensive and complex coronary disease, as well as in those who develop peri-procedure complications, particularly secondary branches occlusion and coronary dissection. The frequency of Tn-I elevation in patients was similar to that observed in other reports.

Future studies are needed with imaging techniques, such as intravascular ultrasound and optical coherence tomography, in order to improve the understanding of the mechanisms responsible for the presence of post-PCI myonecrosis, as well as prospective controlled studies with larger samples, with the final goal to confirm currently existing evidences and to develop new therapeutic strategies in order to improve the prognosis in these patients.

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