Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Thrombolysis-facilitated primary percutaneous coronary intervention as a therapeutic approach to stent thrombosis

Simcha R. Meisel *, Michael Shochat, Aaron Frimerman, Yaniv Levi, David S. Blondheim, Mark Kazatsker, Lubov Vasilenko, Aya Asif, Avraham Shotan

Heart Institute, Hillel Yaffe Medical Center, Hadera, affiliated to the Rappaport Medical School, The Technion- Israel Institute of Technology, Haifa, Israel

A B S T R A C T

Background: Stent thrombosis is a clinically significant event occurring days to weeks or, infrequently, months or years after percutaneous coronary intervention (PCI). Current therapeutic approach is immediate PCI aimed to recanalize the occluded artery in order to restore flow and diminish irreversible myocardial damage.
Methods: We evaluated the coronary patency, TIMI flow and TIMI myocardial perfusion grade (TMPG) in 6 patients presenting with STEMI due to stent thrombosis treated by thrombolysis followed by immediate PCI. These were compared with control patients treated conventionally by primary PCI.
Results: Immediate or early coronary angiography in the treatment group showed good coronary flow in 5 of 6 implicated arteries, whereas immediate angiography in the control group demonstrated 8 completely occluded coronary arteries of 9 with stent thrombosis. The pre-intervention TIMI flow in the control study group was 0.2 ± 0.5 (median–0), and TMPG was 0.1 ± 0.3 (median–0) compared with 2.1 ± 1.1 (median–2.3, $p < 0.001$) and 1.8 ± 1.0 (median–2, $p < 0.001$) in the treatment group, respectively. This striking difference in the rate of coronary patency, pre-procedural TIMI flow and TMPG, however, did not translate into better cardiac function in the treatment group.
Conclusions: These findings suggest that thrombolysis-facilitated PCI may confer benefit and need not be considered contraindicated when treating stent thrombosis. This therapeutic approach should be evaluated as a viable therapeutic approach to stent thrombosis.

© 2015 Elsevier Inc. All rights reserved.

Stent thrombosis typically is a clinically significant event occurring in patients who have undergone a percutaneous coronary intervention (PCI) with stent implantation several days to weeks or, less frequently, months or years earlier. Often, it is a dramatic clinical event characterized by pronounced ischemic symptoms and marked electrocardiographic changes, generally, ST-segment elevations. Stent thrombosis often entails dour clinical consequences due to substantial myocardial damage, and a risk of death [1–6]. The current therapeutic approach is immediate PCI aimed to recanalize the occluded artery at the site of thrombotic occlusion, in order to restore flow and diminish myocardial damage.

During the past 3 years, 6 patients who were admitted to our cardiac care unit with STEMI due to stent thrombosis were treated by thrombolysis. These patients underwent thrombolysis for stent thrombosis as the attending cardiologist was unaware of this possibility, since local protocol requires expeditious primary PCI as therapy for stent thrombosis. Thrombolytic therapy brought about rapid clinical and electrocardiographic reperfusion in 3 patients. Early coronary angiography in these patients demonstrated reasonable or normal coronary flow

(TIMI flow 2–3). The 3 other patients promptly underwent rescue coronary angiography following thrombolysis, due to seemingly partial clinical or electrocardiographic response. Coronary angiography demonstrated patent culprit artery with good coronary flow in 2 patients. Overall, we have observed good clinical response and very early coronary arterial patency in all but one patient.

We describe the clinical features and angiographic findings of the patients admitted urgently for STEMI caused by stent thrombosis, whose initial treatment was thrombolysis followed by immediate or early coronary angiography. These patients, who were subsequently diagnosed as experiencing stent thrombosis, were compared with a control group of patients in whom stent thrombosis was conventionally treated by primary PCI. Our intention is to show that in the case immediate intervention for stent thrombosis is delayed, thrombolysis followed immediately by angiography is a feasible therapeutic approach.

1. Patients and methods

Local protocol requires expeditious primary PCI as therapy for stent thrombosis. The treatment study group included patients admitted emergently for STEMI due to stent thrombosis, who underwent thrombolysis with streptokinase as primary reperfusion therapy, as the attending cardiologist was unaware of this possibility. According

* Corresponding author at: Heart Institute, Hillel Yaffe Medical Center, Hadera 38100, Israel. Tel.: +972 4 630 4419; fax: +972 4 630 4422.
E-mail address: meisel@hy.health.gov.il (S.R. Meisel).

to our current protocol, thrombolysis is administered to STEMI patients who arrive early (within 3 hours from symptom onset), are hemodynamically stable, and when opting for the interventional approach would have caused unnecessary delay. When administered, thrombolysis should be given, as per current guidelines, within 30 minutes from hospital arrival ("door to needle"). In the absence of clear-cut clinical or electrocardiographic signs of reperfusion or when clinical response is equivocal, rescue PCI is performed. Hence, the attending cardiologists assessing the clinical situation in the treatment patients had decided to administer thrombolysis immediately, missing the possibility of stent thrombosis as the potential cause of the STEMI. The features of these patients were compared with those of a control group of STEMI patients admitted due to stent thrombosis, and treated conventionally by primary PCI.

Baseline characteristics, including risk factors for coronary disease and medications, blood tests, various time intervals and length of hospital stay (LOS) were recorded for each patient. Time-to-needle in the thrombolysis-treated patients was defined as the time elapsed from symptom onset to beginning of intravenous infusion of the thrombolytic agent. Time from symptoms to balloon was defined as the time from symptom onset to the first balloon inflation in the primary PCI-treated patients. Cardiac function was evaluated by echocardiography according to overall LVEF and segmental wall motion abnormalities score index (SWMSI). Myonecrosis was assessed by mean 3-day CPK concentration. TIMI flow and TIMI myocardial perfusion grade (TMPG) prior to and immediately after conclusion of all procedures (2 sets for each study group) were determined by 2 experienced interventional cardiologists. In case of disagreement a third observer was consulted for adjudication.

1.1. Statistical analysis

The Mann–Whitney U test was applied to evaluate the significance of differences in quantitative demographics, co-morbid conditions, blood test and echocardiographic results, and LOS between study groups (treatment and control groups). Differences in the categorical parameters were measured by Fisher exact test (Killip grade, co-morbid conditions). Difference between baseline values and those following the stent thrombosis event within study groups of time intervals, LVEF, and SWMSI was assessed by Wilcoxon Signed Ranks Test. A $p \leq 0.05$ was considered significant. Analysis was performed using SPSS 18 (SPSS Inc., Chicago, Illinois).

2. Results

2.1. Patients

Treatment study group comprised 6 patients admitted emergently between May 2011 and March 2014 with STEMI due to stent thrombosis treated by thrombolysis (Table 1). All treatment group patients previously sustained a myocardial infarction (5 STEMI and one an anterior non-STEMI). These were compared with a control group of 9 reasonably matched patients that presented with stent thrombosis and were treated conventionally by primary PCI. The control patients have also undergone a coronary intervention in the past with stent implantation, mostly for myocardial infarction (six patients for STEMI, two for non-STEMI and one elective PCI). All study patients presented with STEMI when admitted later for stent thrombosis. The patients treated by thrombolysis were characterized by a short time interval between symptom onset and admission (49 ± 25 minutes, median–40 minutes). Resolution of ST segment elevation on the electrocardiogram with disappearance of symptoms was attained very early in 3 patients. Early coronary angiography in these patients demonstrated a patent culprit artery with good coronary flow, and was followed by the definitive coronary intervention. In the 3 other patients rescue coronary angiography was performed soon after completion of the infusion of the thrombolytic

Table 1
Demographics, comorbid conditions, vital signs on presentation, basic blood test results and LOS by study groups.

Variable	Treatment group (n = 6)	Control group (n = 9)
Males (%)	5 (83%)	8 (89%)
Age (median), years	45.8 ± 10.1 (45)	56.8 ± 14.5 (59)
Diabetes mellitus, n (%)	1 (17%)	0 (0%)
Smoking, n (%)	5 (83%)	7 (77%)
Hyperlipidemia, n (%)	4 (67%)	7 (78%)
Hypertension, n (%)	3 (50%)	4 (44%)
S/P AMI prior to initial event, n (%)	2 (33%)	3 (33%)
S/P PCI prior to initial event, n (%)	3 (50%)	4 (44%)
STEMI during initial event	5 (83%)	5 (63%)
Systolic blood pressure (median), mmHg	130 ± 28 (142)	122 ± 21 (126)
Diastolic blood pressure (median), mmHg	83 ± 18 (89.5)	72 ± 13 (70)
Heart rate (median), beats/min	85 ± 18 (86.5)	78 ± 23 (80)
Killip class I, n (%)	5 (83%)	7 (78%)
Creatinine (median), mg%	0.86 ± 0.25 (0.86)	0.84 ± 0.16 (0.91)
Hemoglobin (median), gr/dl	14.9 ± 1.1 (14.7)	13.8 ± 2.2 (13.9)
White blood cell count ($\times 10^3$ cells/mm^3)	11.9 ± 2.3 (11.8)	9.7 ± 3.5 (8.9)
Platelet count ($\times 10^3$ cells/mm^3)	237 ± 57 (243)	207 ± 64 (206)
Cholesterol (median), mg%	200 ± 32 (195)	162 ± 43 (162)
LDL (median), mg%	132 ± 32 (132)	98 ± 37 (93)
HDL (median), mg%	36 ± 17 (33)	49 ± 15 (47)
TG (median), mg%	160 ± 71 (151)	82 ± 49 (60)*
Troponin T (median), ng/ml	0.4 ± 0.6 (0.2)	1 ± 0.8 (1)
Mean CPK (units/liter)	348 ± 256 (226)	849 ± 741 (763)

* p = 0.05, all other p = NS.

agent, despite amelioration of symptoms, due to lack of complete ST segment resolution. In 2 of these patients a patent culprit coronary artery with TIMI flow 2–3 was observed, while an occluded LAD was demonstrated in the third patient. A PCI was performed in all cases (Table 2). Of this group 2 patients died: one during the admission for stent thrombosis in the LAD following a failed coronary intervention, and the second patient who sustained significant myocardial damage died 2 months following admission for stent thrombosis.

2.2. Time intervals

Time intervals for the initial admission in both study groups are presented in Table 2. Time intervals for the admission of stent thrombosis

Table 2
Time intervals, blood tests, coronary TIMI flow and perfusion, cardiac function, and LOS of admission for stent thrombosis by study groups.

Variable	Treatment group (thrombolysis) at stent thrombosis N = 6	Control group (conventional) at stent thrombosis N = 9
Symptoms-to-ED (mins)	49 ± 25 (40)	103 ± 62 (93)
Pain-to-balloon time (mins)	I/R	277 ± 126 (239)
Door-to-balloon time (mins)	I/R	122 ± 49 (127)
Door-to-needle time (mins)	45 ± 31 (33)	I/R
Mean CK (U/liter)	334 ± 184 (244)	591 ± 356 (490.7)
Initial WBC count (cell/mm^3)	16200 ± 4700 (17200)	12300 ± 4100 (11400)
Initial platelet count (cell/mm^3)	269 ± 69 (286)	281 ± 147 (235)
LVEF (%)	48 ± 12% (48)	49 ± 17% (48)
SWMSI	1.7 ± 0.5 (1.5)	1.7 ± 0.6 (1.5)
IRA Stenosis < 75% at presentation	4 (66%)	0 (0%) *
Patent IRA (TIMI flow ≥ 2) at presentation	5 (84%)	1 (11%) ***
%TMPG > 2 at presentation	3 (50%)	0 (0%) **
Culprit coronary artery	RCA-4, LAD-2	RCA-6, CRX-1, LAD-2
Hospital LOS (days)	3.3 ± 2.3 days (3.5)	3.9 ± 2.6 days (3.5)

Numeric values are represented as mean ± STD (median), categorical variables as numbers (percentage). SWMSI = segmental wall motion abnormalities score index, IRA = infarct-related artery, LOS = length of stay, I/R = irrelevant.
 * p ≤ 0.01.
 ** p < 0.05.
 *** p = 0.002, all other variables non-significant.