Journal of Clinical & Experimental Cardiology
ISSN: 2155-9880

Huang, et al., J Clin Exp Cardiolog 2016, 7:2
DOI: 10.4172/2155-9880.1000419

Research Article Open Access

A Small Sample Retrospective Study of Non-Infarct-Related Artery Simultaneous Revascularization during Primary Percutaneous Coronary Intervention for St-Segment Elevation Myocardial Infarction

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Received date: 01 February, 2016; **Accepted date:** 16 February, 2016; **Published date:** 26 February, 2016

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Abstract

Objective: In patients with acute myocardial infarction (AMI) and multivessel coronary disease undergoing primary percutaneous coronary intervention (PCI), we compare the major cardiovascular events and plasma inflammatory markers (hsCRP, sCD40L, IL-6, and TNF-a) after treatment with simultaneous complete revascularization or culprit-only primary angioplasty.

Method: From June 2011 to June 2014, a total of 74 patients with AMI and multivessel coronary disease in our hospital underwent primary PCI, and among them 24 (32%) patients underwent simultaneous complete revascularization (complete PCI group) and 50 (68%) patients underwent culprit-only primary angioplasty (culprit-only group), then underwent PCI for the non-infarct-related artery at 1-4 weeks after primary PCI. The outcome was compared between the two groups one year after treatment.

Result: There was no significant difference in the incidence of major adverse cardiovascular events (non-fatal myocardial infarction, target vessel repeat revascularization, and cardiac death) between the two groups at one year ($P > 0.05$). The changes of these inflammatory markers were not statistically significant between the two groups ($P > 0.05$).

Conclusion: Compared to the culprit-only group, the complete PCI group had similar incidences of major adverse cardiovascular events (non-fatal myocardial infarction, target vessel repeat revascularization, all-cause and cardiac mortality). The present study suggests it was safe to intervene the non-infarct-related artery simultaneously during primary PCI.

The elevated inflammatory marker levels were reduced in both groups, but the changes of these markers were not significantly different, so the long-term effects of these two PCI procedures are similar.

Keywords: Acute ST-segment elevation myocardial infarction; Percutaneous coronary intervention; Non-infarct-related artery; Major adverse cardiovascular events; Plasma inflammatory markers

Introduction

Acute myocardial infarction (AMI) is one of the major threats to global human health [1-5]. Acute ST-segment elevation myocardial infarction (STEMI) is the most severe AMI. Currently, percutaneous coronary intervention (PCI) has become a major measure for AMI and an important method of coronary revascularization [6]. Statistics show that, in patients with AMI, multivessel disease accounts for as much as 40-50% [7]. Compared with the patients with single-vessel disease, patients with multivessel disease generally have a longer history of coronary heart disease; higher rates of complicating hypertension, diabetes, and hyperlipidemia; more serious clinical symptoms caused by myocardial ischemia; increased postoperative complications; significantly higher mortality; and poorer prognosis [8-10].

Most previous studies do not support non-infarct-related artery revascularization during primary PCI in emergency situations for STEMI patients with multivessel disease. The majority of guidelines recommend primary intervention of the infarct-related artery for patients with AMI, and non-infarct-related artery intervention will only be considered in patients with cardiogenic shock [11-14]. However, in recent years there has been controversy around whether non-infarct-related artery revascularization needs to be conducted during primary PCI for STEMI patients with multivessel disease, because some research has shown that non-infarct-related artery revascularization during PCI intervention for STEMI patients with multivessel disease is beneficial [15-20].

In the clinical setting, non-infarct-related artery revascularization is being conducted in some patients during primary PCI. These patients' short, long-term prognosis is still a question.

Inflammatory markers can be used to identify the increased risk of cardiovascular events, and are helpful when evaluating the prognosis

of acute coronary syndrome. Whether inflammatory markers can be used to guide the selection of therapeutic strategies in STEMI patients with multivessel disease is unreported.

This study is a retrospective small sample size controlled study. These included STEMI patients with multivessel coronary disease divided into complete PCI group and culprit-only PCI group according to simultaneous complete revascularization or culprit-only primary angioplasty during primary PCI. We compared one-year clinical endpoint events and the levels of inflammatory markers, evaluated the impact of different treatment strategies for the prognosis. The aim of this study is to provide a basis for selection of treatment strategies for these patients.

Subjects and Methods

Subjects

Included in our study were 74 patients with initial acute STEMI who received PCI from June 2011 to June 2014 at Gongli hospital affiliated with Shanghai Second Military Medical University.

Patients who met the inclusion criteria were aged 35 to 85 years old, male or female, who had experienced STEMI and received successful emergency PCI within 12 hours of onset. Diagnostic criteria for STEMI were chest pain within 12 hours accompanied by two or more contiguous chest lead ST segment elevation of ≥ 0.2 mV or limb leads ST segment elevation of ≥ 0.1 mV, or new onset left bundle branch block with or without elevated markers of myocardial injury.

Patients were excluded if unsuitable for undergoing primary PCI or in cases of rejected PCI or primary PCI failure (see PCI success criteria below); a history of myocardial infarction; left main coronary artery disease; chronic occlusion; multivessel occlusion; coronary artery severe disease and calcification; severe liver or kidney dysfunction; cancer; or if the patient died during hospitalization.

Participants were divided into a complete PCI group (n = 24) and a culprit-only PCI group (n = 50) according to simultaneous complete revascularization or culprit-only primary angioplasty during primary PCI. In the culprit-only PCI group, the PCI procedure on the non-infarct-related artery was conducted within 1 to 4 weeks after primary PCI, which included the hospitalization period and after discharge.

Research Methods

Pre-PCI preparation in the emergency department and PCI procedure

After signing the informed consent forms for PCI, all patients chew enteric-coated aspirin (300 mg) and clopidogrel (600 mg) before the PCI procedure. After the PCI procedure, the patients were administered aspirin (100 mg/d) and clopidogrel (75 mg/d). During the PCI procedure, unfractionated heparin (50-70 U/kg) was given to the patients. After the PCI procedure, patients took low-molecular-weight heparin (70-100 U/kg) for 12 hours per day for 3-5 days. The left and right coronary angiography were performed using Judkins technique to determine the infarct-related artery (IRA) and conduct balloon dilation and stenting for the IRA (and non-IRA in some patients) or direct coronary stenting.

PCI success criteria

In the images of coronary angiography using at least two mutually perpendicular projection planes, residual diameter stenosis is less than 20% post-stenting. A post-PCI TIMI flow grade [21] is 2 - 3 with no serious cardiovascular adverse events during the PCI procedure (death, stroke, endotracheal intubation, need emergency coronary artery bypass graft, severe complications of PCI such as severe coronary dissection, tearing, perforation, hemorrhage, cardiac rupture, etc.) is considered a successful PCI.

Data collection and treatment after primary PCI

Data from the two groups of patients were collected after being admitted to our hospital. All patients underwent serum inflammatory markers (hsCRP, IL-6, TNF-a, sCD40L) tests at 24 hours after primary PCI. The patients in the culprit-only PCI group underwent PCI for non-infarct-related arteries at 1-4 weeks after primary PCI, including hospitalization period and after discharge. If no contraindications were reported, the patients in the two groups were given dual antiplatelet drugs, statins, ACEI/ARB, and β-blockers for combination therapy.

Follow-up after discharge

Follow-up with the patients occurred at the outpatient clinic for coronary stents for one year or until death. During the follow-up, major adverse cardiovascular events (MACEs) were recorded, which include recurrent myocardial infarction, target vessel repeat revascularization, all-cause, and cardiac death.

Test of serum inflammatory markers

Serum inflammatory markers (hsCRP, IL-6, TNF-a, sCD40L) tests were conducted in all survival subjects at 12 months after primary PCI, and the relationship between biomarkers and clinical outcome were analyzed.

Statistical analysis

SPSS l8.0 statistical software was used for analysis. Quantitative data were expressed in $\bar{x} \pm S$. Comparisons between groups were made with the t test and one-way analysis of variance; enumeration data were compared with χ^2 test. $P < 0.05$ was considered statistically significant.

Results

Baseline parameters of two groups

A total of 74 patients were included, with 24 patients in the complete PCI group and 50 patients in culprit-only PCI group. Comparison of baseline characteristics between the two groups did not show significant differences (Table 1). Further, no significant difference was shown between the two groups in symptom onset-to-balloon time, door-to-balloon time, coronary lesions, stent implantation, pre-PCI thrombolysis in myocardial infarction (TIMI) flow grade, post-PCI TIMI flow grade, pre-PCI minimal lumen diameters, and post-PCI minimum lumen diameter ($P > 0.05$) (Table 2).

	Complete PCI group	Culprit only PCI group	χ2 value or t value	P Value
	(n=24)	(n=50)		

Age (years)	61.62 ± 10.17	62.82 ± 10.38	1.12*	0.765
Gender (Male) (%)	19 (79.1)	41 (82)	0.09	0.771
History of hypertension (%)	20 (83.3)	42 (84)	0.01	0.942
History of diabetes (%)	14 (58.3)	30 (60)	0.02	0.891
Smoking history (%)	17 (70.8)	36 (72)	0.01	0.917
Family history of coronary heart disease (%)	4 (16.7)	8 (16)	0.01	0.942
Glucose mmol/l	7.15 ± 1.23	7.23 ± 1.35	-0.74*	0.736
Cholesterol mmol/l	4.58 ± 1.26	4.60 ± 1.35	2.23*	0.157
High-density lipoprotein mmol/l	0.92 ± 0.33	0.94 ± 0.22	-0.42*	0.149
Low-density lipoprotein mmol/l	3.20 ± 1.07	3.19 ± 1.04	0.77*	0.333
Triglyceride mmol/l	1.82 ± 1.04	1.81 ± 1.06	1.69*	0.282
Creatinine umol/l	73.13 ± 43.15	72.12 ± 43.23	3.57*	0.978
CKMB ug/l	177.68 ± 78.28	178.56 ± 78.34	-2.26*	0.958
cTnI ng/ml	17.28 ± 9.36	17.15 ± 9.22	1.56*	0.698
Left ventricular ejection fraction (%)	57.39 ± 4.65	57.23 ± 4.59	-2.85*	0.697
Killip class III/IV at admission (%)	3 (12.5)	6 (12)	0	0.951
Statins (%)	22 (91.7)	45 (90)	0.05	0.819
ACEI (or ARB) (%)	19 (79.1)	41(82)	0.09	0.771
BB (%)	19 (79.1)	40 (80)	0.01	0.933
ASA (%)	21 (87.5)	46 (92)	0.38	0.536
Clopidogrel (%)	22 (91.7)	48 (96)	0.6	0.440

Note: *means t value, all others are χ^2 value; ACEI (ARB): angiotensin-converting enzyme inhibitors (angiotensin II receptor antagonist); BB: Beta Blockers; ASA: Aspirin; CKMB: creatine kinase MB; cTnI: cardiac troponin I

Table 1: Comparison of baseline characteristics of the two groups of patients.

	Complete PCI group	**Culprit only PCI group**	**χ2 value or t value**	**P Value**
	(n=24)	**(n=50)**		
2 vessel disease (number, %)	12 (50)	27 (54)	0.1	0.747
3 vessel disease (number, %)	12 (50)	23 (46)	0.1	0.747
IRA site (number, %)				
LAD (left anterior descending artery)	7 (29.1)	17 (34)	0.17	0.678
LCX (left circumflex artery)	7 (29.1)	19 (38)	0.56	0.456
RCA (right coronary artery)	10 (41.7)	22 (44)	0.04	0.85
Total occlusion of IRA (number, %)	18 (75)	37 (74)	0.01	0.927
Non-IRA site (number, %)				
LAD (left anterior descending artery)	9 (37.5)	18 (36)	0.03	0.853
LCX (left circumflex artery)	11 (45.8)	23 (46)	0	0.989
RCA (right coronary artery)	12 (50)	24 (48)	0.03	0.872
SOTB (h, x ± s)	8.8 ± 7.4	8.9 ± 7.5	1.88*	0.465
D2B (min, x ± s)	85.0 ± 29.4	85.0 ± 31.5	-0.55*	0.412
Pre-PCI TIMI flow (number, %)				
Grade 0-1	18 (75)	40 (80)	0.24	0.625
Grade 2	5 (20.8)	8 (16)	0.26	0.609
Grade 3	1(4.2)	2(4)	0	0.973
Post-PCI TIMI flow (number, %)				
Grade 2	4(16.7)	612	0.3	0.583
Grade 3	20 (83.3)	44(88)	0.3	0.583

Note: * means t value, all others are χ^2 value; SOTB: symptom onset-to-balloon time; D2B: door-to-balloon time; IRA: infarct-related artery.

Table 2: Comparison of coronary artery lesions in two groups at emergency visit.

Comparison of cardiovascular event incidence rate

All subjects received clinical follow-up, with an average follow-up time of 360 ± 17 days. During the average 12 months of post-PCI follow-up, one patient in the complete PCI group died of heart failure, one patient in culprit-only PCI group died of cancer, and two patients in culprit-only PCI group died of heart failure. MACEs (recurrent myocardial infarction, revascularization of target-vessel, all-cause, and cardiac death) in the one year of follow-up were not significantly different between the two groups (all P > 0.05) (Table 3).

	Complete PCI group	**Culprit only PCI group**	**χ2**	**P Value**
	(n=24)	**(n = 50)**		
All-cause death (number, %)	1 (4.2)	3 (6)	0.11	0.744

Cardiac death (number, %)	1 (4.2)	2 (4)	0	0.973
Recurrent myocardial infarction (number, %)	1 (4.2)	2 (4)	0	0.973
Repeat revascularization (number, %)	3 (12.5)	6 (12)	0	0.951
Repeat PCI	2 (8.3)	5 (10)	0.05	0.819
Repeat PCI for IRA	1 (4.2)	2 (4)	0	0.973
Repeat PCI for non-IRA	0 (0)	1 (2)	0.49	0.485
PCI for other vessels	1 (4.2)	2 (4)	0	0.973
Coronary artery bypass graft	1 (4.2)	1 (2)	0.29	0.591
MACEs (number, %)	5 (20.8)	11 (22)	0.01	0.909

Table 3: Comparisons of incidence of major adverse cardiovascular events during one year follow-up in two groups.

Test results of inflammatory markers

There was no statistically significant difference of baseline inflammatory markers ($P > 0.05$) between the two groups post-PCI (Table 4). After exclusion of those who died and repeat-revascularization patients, there was no statistically significant difference in inflammatory factors at one year post-PCI ($P > 0.05$) (Table 5). Further, there was no significant difference between the two groups' inflammatory markers before and after PCI ($P > 0.05$) (Table 6). The inflammatory markers levels were significantly reduced post-PCI compared with pre-PCI in both groups ($P < 0.05$).

	Complete PCI group	**Culprit only PCI group**	**t value**	**P Value**
	(n = 24)	**(n = 50)**		
hsCRP (mg/l)	85.77 ± 24.13	98.17 ± 23.97	-2.43	0.49
sCD40 L (ng/ml)	15.62 ± 6.99	14.51 ± 5.25	1.46	0.21
IL-6 (pg/ml)	14.25 ± 1.09	12.75 ± 1.68	1.37	0.28
TNF-a (pg/ml)	239.55 ± 38.43	228.1 ± 26.33	1.98	0.57

Table 4: Comparison of baseline levels of inflammatory markers in two groups.

	Complete PCI group (n = 20)	**Culprit only PCI group (n = 42)**	**t value**	**P Value**
hsCRP (mg/l)	75.33 ± 22.41	75.19 ± 22.87	0.52	0.65
sCD40 L (ng/ml)	10.56 ± 4.09	9.52 ± 4.35	1.23	0.34
IL-6 (pg/ml)	9.31 ± 1.24	8.78 ± 1.49	0.67	0.54
TNF-a (pg/ml)	101.18 ± 17.33	118.17 ± 17.38	-0.54	0.49

Table 5: Comparisons of inflammatory markers in two subgroups at 1 year later.

Discussion

There has been controversy among researchers on the selection of treatment strategy in coronary multivessel disease; in particular, whether STEMI patients should undergo simultaneous complete revascularization or culprit-only primary angioplasty during primary PCI has become the focus of debate. A HORIZONS - AMI study has shown that when STEMI patients underwent primary PCI and simultaneous complete revascularization was conducted, recent and long-term mortality increased, and chronic heart failure, stent thrombosis, and shock also increased [22]. Some studies also showed that simultaneous complete revascularization does not improve prognosis or reduce the incidence of MACEs [12,23-25]. For patients with AMI, multivariate regression analysis showed that undergoing simultaneous complete revascularization is an independent risk factor for MACEs. Most of the clinical meta-analysis does not support simultaneous intervention of the non-infarct-related artery during acute myocardial infarction.

	Complete PCI group (n = 20)	**Culprit only PCI group (n = 42)**	**t value**	**P Value**
hsCRP (mg/l)	21.09 ± 12.34	19.32 ± 10.44	0.97	0.53
sCD40 L (ng/ml)	5.57 ± 3.21	4.78 ± 2.24	1.27	0.29
IL-6 (pg/ml)	3.51 ± 1.36	4.25 ± 1.89	-1.56	0.69
TNF-a (pg/ml)	116.92 ± 23.55	121.11 ± 21.22	-2.46	0.37

Table 6: Comparisons of changes in inflammatory markers in two subgroups.

However, some studies have shown that simultaneous complete revascularization will reduce MACEs and significantly decrease hospital mortality compared with culprit-only PCI [16]. Navarese et al.'s study also found that simultaneous complete revascularization may reduce repeat revascularization when compared with culprit-only primary angioplasty, but does not reduce mortality or the incidence of recurrent myocardial infarction [17]. In the 2013 annual ESC meeting, the results of PRAMI research released showed that during a 23-month mean follow-up period, MACEs was reduced by 65% in complete revascularization patients than culprit-only primary angioplasty patients during primary PCI [17]. The CvLPRIT study that was released at the 2014 annual ESC meeting reached a similar conclusion [19], finding that the outcomes in simultaneous complete revascularization patients are much better than culprit-only primary angioplasty patients during primary PCI at one year after PCI, and composite end points reduced significantly at 55%, including all-cause death, recurrent myocardial infarction, heart failure, and repeat revascularization (10.0% vs 21.2%, $P = 0.009$). At the EuroPCR 2015 congress, the results of the PRAGUE study were released. The study included 214 STEMI patients with severe stenosis of multivessel non-culprit coronary arteries ($\geq$ 70%) randomly divided into complete revascularization group (n = 106) and culprit-only primary angioplasty group (n = 108), with a mean follow-up period of 38 weeks. The results showed no significant difference between the two groups in either the composite end point or the individual end points of all-cause death, nonfatal myocardial infarction, and stroke [20].

In our study, which included 74 patients, there was no significant difference in baseline characteristics and inflammatory marker data between the emergency coronary angiography and primary PCI

groups (P > 0.05). No significant differences in major adverse cardiovascular events were found between the complete PCI group and culprit-only PCI group (P > 0.05) in an average 12-month follow-up after PCI. Our results suggest that simultaneous complete primary PCI for STEMI patients is safe without additional cardiovascular-related events. This conclusion is similar to the results reported by the PRAMI [18], CVLPRIT [19] and PEAGUE studies [20]. As for simultaneous primary complete PCI-related reduced incidence of cardiac death, nonfatal myocardial infarction, and angina found in PRAMI study, we did not find the same results in our study. We also did not find simultaneous complete PCI-related reduced incidence of all-cause mortality, recurrent myocardial infarction, heart failure, and repeat revascularization incidence as found in CvLPRIT study. Our study results are similar to the neutral conclusion in the PEAGUE study. However, in the PEAGUE study, most patients underwent complete revascularization at 3-40 days after primary PCI, and only a few patients underwent complete revascularization at primary PCI, so comparing our results with those of the PEAGUE study is questionable.

Inflammatory markers, including hsCRP, IL-6, TNF-a and sCD40 L, have received attention in recent years. A number of studies show that the level of baseline HsCRP can predict the occurrence of future cardiovascular events [26]. A case study of 2539 ACS patients without ST segment elevation showed that patients with higher sCD40 L levels have the 2.5 fold incidence of myocardial infarction [27,28]. Studies have shown that serum TNF-a levels were significantly higher in unstable angina and stable angina patients than in healthy people [29,30]. IL-6 level is an independent predictor of long-term risk of myocardial infarction in healthy people [31,32]. In our study, 62 patients without repeat revascularization underwent repeat tests for inflammatory markers. The comparison of baseline inflammatory markers after PCI and inflammatory markers one year later in the two groups did not show significantly differences (P > 0.05). The inflammatory markers one year later were significantly decreased compared with baseline levels (P < 0.05) in both groups while the changes of inflammatory markers in two groups were not significantly different (P > 0.05). This result is due to standard drug treatment of coronary heart disease. The lipid-dependent or non-lipid- dependent anti-inflammatory effect of statins cannot be ignored. One study found that statins play an anti-inflammatory effect primarily by reducing inflammatory markers and inhibition of adhesion molecules [33]. These anti-inflammatory effects of statins may be associated with upregulation of endothelial NO production and inhibiting the release of superoxide. Moreover, statins can reduce the expression of CD40 and reduce myocardial cell activity related to CD40 [34]. Luisa et al. [35] found that short-term use of statins not only reduces HMG-CoA reductase activity without affecting plasma cholesterol levels but also inhibits lipopolysaccharide and carrageenan-induced aggregation of leukocytes as well as the production of interleukin-6 (IL-6) and MCP-1. Further research suggests that statins regulate the production of cytokine and chemokine by non-steroid compounds converted by mevalonate synthesis, and that statins inhibit the inflammatory response independently of lowering cholesterol. Massy et al. found that lovastatin can reduce the expression and secretion of interleukin-6 in human renal cells, and this is dose-dependent to low-density lipoprotein and oxidized LDL. The effect of lovastatin can be partially eliminated by mevalonate [36].

Since this study was a retrospective, non-randomized study of a small sample size, our results need to be confirmed by prospective, randomized control studies with larger sample sizes with longer follow-up times.

Grant support

This study was supported by grants from Jiangsu Province's Outstanding Medical Academic Leader program (No.LJ201140) and the Health Science and Technology Key Cooperation Projects of Department of Social Development, Pudong District, Shanghai (No. PW2009D-2).

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