

Cardioprotective Effects of Intracoronary Morphine in ST-Segment Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention: A Prospective, Randomized Trial

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Background—A cardioprotective role of morphine acting via opioid receptors has been demonstrated, and previous preclinical studies have reported that morphine could reduce reperfusion injury and myocardial infarct size in a way similar to that of ischemic preconditioning. This study aimed to evaluate the effect of intracoronary morphine on myocardial infarct size in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention.

Methods and Results—This study was designed as a 2-center, prospective, randomized, open-label, blinded end point trial. A total of 91 ST-elevation myocardial infarction patients with thrombolysis in myocardial infarction flow grade of 0 to 1 undergoing primary percutaneous coronary intervention were randomly assigned to a morphine or control group at a 1:1 ratio. The morphine group received 3 mg of morphine sulfate diluted with 3 mL of normal saline, and the control group received 3 mL of normal saline into a coronary artery immediately after restoration of coronary flow. The primary end point was myocardial infarct size assessed by cardiac magnetic resonance imaging. The cardiac magnetic resonance images were evaluated for 42 and 38 patients in the morphine and control groups, respectively. Myocardial infarct size was not different between the 2 groups ($25.6 \pm 11.2\%$ versus $24.6 \pm 10.5\%$, $P=0.77$), nor was the extent of microvascular obstruction or myocardial salvage index ($6.0 \pm 6.3\%$ versus $5.1 \pm 4.6\%$, $P=0.91$; $31.1 \pm 15.2\%$ versus $30.3 \pm 10.9\%$, $P=0.75$, respectively). There was no difference in peak creatine kinase-MB level, final thrombolysis in myocardial infarction flow, myocardial blush grade, or complete resolution of ST-segment.

Conclusions—Intracoronary morphine administration could not reduce myocardial infarct size in ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention.

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Key Words: cardiac magnetic resonance imaging • intracoronary morphine • percutaneous coronary intervention • reperfusion injury • ST-segment elevation myocardial infarction

Since the introduction of primary percutaneous coronary intervention (PCI), the mortality of ST-segment elevation acute myocardial infarction (STEMI) has been dramatically

reduced to below 10%.¹ However, a significant number of patients are still at risk for cardiac death or heart failure due to left ventricular systolic dysfunction.² This is because blood

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Accompanying Tables S1 and S2 are available at <http://jaha.ahajournals.org/content/6/4/e005426/DC1/embed/inline-supplementary-material-1.pdf>

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flow restoration in the epicardial coronary artery is not identical to myocardial perfusion, and myocardial perfusion may be more important.^{3,4} Myocardial damage occurs not only during the ischemic period but also during reperfusion; this is called reperfusion injury. The benefit of reperfusion is limited by this phenomenon during the first few minutes after restoration of blood flow.^{5,6} Recently, several strategies have been attempted to reduce reperfusion injury and myocardial infarct size.⁷ Among several pharmacological agents, morphine has demonstrated a cardioprotective effect via opioid receptors, and previous laboratory and animal studies have reported that morphine could reduce reperfusion injury and myocardial infarct size in a way similar to that of ischemic preconditioning.⁸⁻¹⁰ However, to date, limited data are available on the cardioprotective effects of morphine in STEMI.

Regarding route of administration, several studies have suggested that intracoronary injection of cardioactive drugs showed superior efficacy compared with intravenous application.¹¹⁻¹³ Morphine may be more protective against reperfusion injury by intracoronary injection compared with intravenous injection. Therefore, we conducted a randomized trial to compare the effects of intracoronary morphine administration on myocardial infarct size in STEMI patients undergoing primary PCI using cardiac magnetic resonance imaging (CMR).

Methods

Study Design and Patients

This study was designed as a 2-center, prospective, randomized open-label, blinded end point study. The study incorporated 2 sequential randomized phases to allow a comparison of ticagrelor with clopidogrel and a comparison of intracoronary morphine with intracoronary saline with regard to myocardial infarct size. Eligible patients were those who had STEMI and planned primary PCI. Inclusion criteria were the presence of chest pain for less than 12 hours after symptom onset and ST-segment elevation of more than 1 mm in more than 2 contiguous leads. We excluded patients with the following features: (1) hemodynamic instability; (2) rescue PCI after thrombolysis or facilitated PCI; (3) noncardiac comorbidities with life expectancy of <1 year or that might result in protocol noncompliance according to the investigator's medical judgment; (4) female of childbearing potential, unless a recent pregnancy test was negative, or planning to become pregnant any time after enrollment; (5) contraindications to study medications or contrast agent; (6) receiving clopidogrel 300 mg or more before the first randomization; (7) a history of previous myocardial infarction; or (8) contraindications to CMR. Hemodynamic instability

was defined as cardiogenic shock, respiratory failure, ventricular tachyarrhythmias requiring electrical cardioversion or defibrillation, or any situation in need of cardiopulmonary resuscitation or percutaneous cardiopulmonary support. The protocol was approved by the local institutional review board, and written informed consent was obtained from all participants. The study protocol was registered at clinicaltrials.gov (NCT01738100).

Randomization and Study Procedures

The first randomization assigned patients to the ticagrelor group or the clopidogrel group in a 1:1 ratio. In the ticagrelor group patients received a 180-mg loading dose followed by a maintenance dose of 90 mg twice daily. In the clopidogrel group, patients received a 600-mg loading dose followed by a daily maintenance dose of 75 mg. The results of the comparison between P2Y₁₂ inhibitors will be reported elsewhere. The second randomization was performed after diagnostic angiography. Patients with a thrombolysis in myocardial infarction (TIMI) flow grade of 0 or 1 in the culprit vessel were randomly assigned to receive a bolus intracoronary (IC) injection of either morphine sulfate or saline at a 1:1 ratio. Randomization was performed with a web-based response system (www.ecrf.kr/tica) and stratified by the enrollment site and infarct location (anterior or nonanterior).

All patients received 300 mg of aspirin unless they had previously taken this medication. Intravenous heparin was administered to maintain an activated clotting time of >250 seconds. Coronary angiography and stent implantation were performed using standard interventional techniques. Thrombus aspiration, balloon predilation and postdilation, type of stents, use of glycoprotein IIb/IIIa inhibitors, and intravascular imaging were left to the operators' discretion. In the IC morphine group, 3 mg of morphine sulfate diluted with 3 mL of normal saline was injected into a coronary artery immediately after restoration (TIMI grade ≥ 2) of coronary flow regardless of the method of restoration. In the control group, patients received an IC injection of 3 mL normal saline instead.

The myocardial band fraction of creatine kinase (CK-MB) was measured before PCI and every 8 hours for 2 days after the index procedure. Then CK-MB was measured once daily until the level was normalized. Twelve-lead ECGs were obtained before and 30 minutes after the procedure. The definition of complete ST-segment resolution was a decrement in the sum of ST-segment elevation of 70% or more.¹⁴ TIMI flow and myocardial blush grades were evaluated by standard methods.¹⁵ ECG and angiographic analyses, which included postprocedural TIMI flow grade, myocardial blush grade, and complete ST-segment resolution at 30 and

60 minutes after the procedure, were performed by 2 independent observers blinded to the study group assignment.

Both groups received 100 mg of aspirin daily. We recommended optimal pharmacological therapy in all patients, which included statins, β -blockers, or renin-angiotensin system blockers according to current guidelines.¹⁶

Cardiac Magnetic Resonance Imaging and Analysis

CMR was performed within 5 days after the index event, and CMR images were acquired on a 1.5-T scanner (Magnetom Avanto, Syngo MR B15 version; Siemens Medical Solutions, Erlangen, Germany) with a 32-channel phased-array receiver coil. Cine images were acquired using a steady-state free-precession sequence with 8 to 10 contiguous short-axis slices to cover the entire left ventricle (LV) with a slice thickness of 6 mm and a 4-mm gap. T2-weighted imaging was performed in the continuous short-axis direction using a dark-blood inversion recovery fast-spin echo sequence before contrast was administered. A phase-sensitive inversion recovery technique was used for standard delayed gadolinium-enhanced imaging. The field of view and image matrix were 35×35 and 256×256 cm, respectively.

All measurements were performed at our CMR core laboratory by an experienced observer blinded to patient data using commercialized software (CAAS MRV version 1.0, Pie Medical Imaging BV, Maastricht, The Netherlands). Infarct size was defined as the proportion of delayed hyperenhancement to LV myocardial volume, and hypoenhanced region surrounded by a hyperenhanced area was considered a sign of microvascular obstruction (MVO).¹⁷ The myocardial salvage index was calculated as (area-at risk—infarct size)×100/area-at risk. Transmural infarct extent was expressed as a percentage of infarct thickness and categorized into 5 transmural scores. Infarct thickness was defined as the enhanced wall thickness/total wall thickness of the infarct LV segment. A transmural score was categorized according to infarct thickness: 0, no infarction; 1, 1% to 25%; 2, 26% to 50%; 3, 51% to 75%; and 4, 76% to 100% of wall thickness. The mean infarct transmural score was calculated by dividing the sum of hyperenhancement segmental scores by the number of segments with any delayed hyperenhancement.¹⁸

Study End points

The primary end point was myocardial infarct size (percentage LV volume) assessed by CMR. Secondary end points included the extent of MVO and myocardial salvage index, postprocedural TIMI flow grade, myocardial blush grade, complete ST-segment resolution at 30 minutes after the procedure, and peak CK-MB level. The definition of complete ST-segment

resolution was a decrement in the sum of ST-segment elevation of 70% or more.¹⁴ TIMI flow and myocardial blush grades were evaluated by standard methods.¹⁵ ECG and angiographic analyses, which included postprocedural TIMI flow grade, myocardial blush grade, and complete ST-segment resolution at 30 and 60 minutes after the procedure, were performed by 2 independent observers blinded to study group assignment. In-hospital complications after primary PCI included death, intra-aortic balloon pump use, acute pulmonary edema, bleeding, recurrent ischemia, stent thrombosis, arrhythmias, stroke, or infection. Major adverse cardiac events included death, MI, and hospital readmission for heart failure at 6 months based on the definition used in our previous study.¹⁴

Statistical Analysis

The expected SD for myocardial infarct size was estimated to be 10% based on the previous study, and a relative reduction of 30% in infarct size from 25% to 17.5% was considered significant.^{13,15} For a power of 0.90 and an α error of 0.05, the estimated sample size needed to be 38 patients in each group. The final sample size of 45 was chosen to account for up to 15% unavailable CMR studies in each group. The Statistical Analysis Software package (SPSS Inc, Chicago, IL) was used for all analyses. Continuous variables were expressed as the median and interquartile range or the mean±SD and compared using t test or Mann-Whitney U nonparametric test as appropriate. Categorical variables were expressed as counts or percentages and analyzed using Pearson chi-squared or Fisher exact tests. We also performed subgroup analyses to evaluate the consistency of treatment effects of morphine using generalized linear models. All tests were 2 sided, and *P* values less than 0.05 were considered statistically significant.

Results

Baseline Characteristics

During the study period, a total of 110 patients undergoing primary PCI were randomly assigned to the ticagrelor group or the clopidogrel group. Of these, 91 patients with TIMI flow grade of 0 to 1 were randomly assigned to the IC morphine group (n=45) or the control group (n=46). We excluded patients with symptom-to-balloon time more than 12 hours (n=1), previous history of myocardial infarction (n=1), hemodynamic instability (n=1), concurrent brain tumor (n=1), withdrawal from the trial (n=3), or refusal to CMR (n=4). Finally, CMR could be evaluated in 42 patients in the IC morphine group and 38 patients in the control group

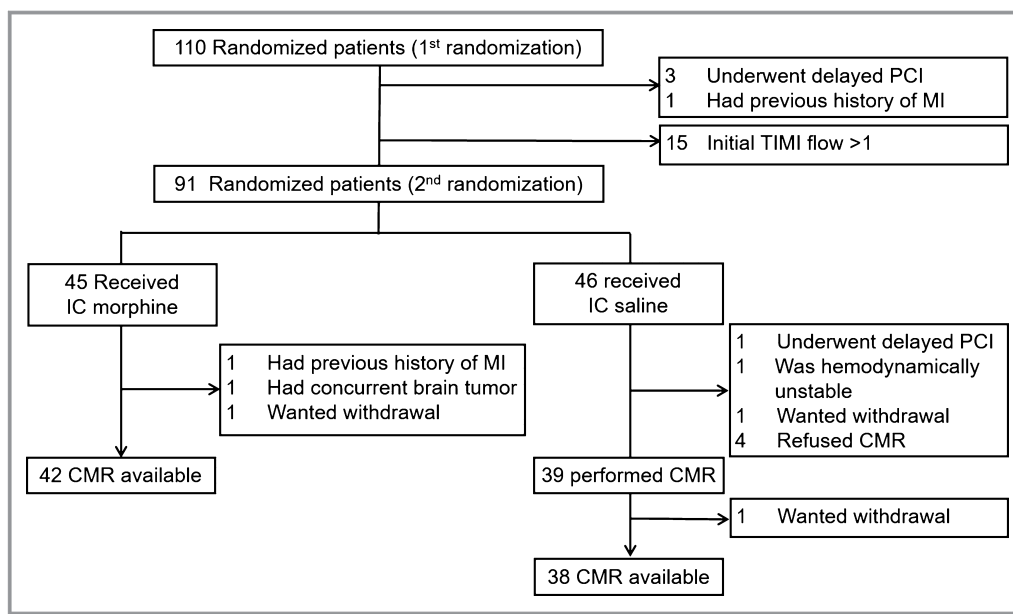


Figure 1. Study flow. CMR indicates cardiac magnetic resonance; IC, intracoronary; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

(Figure 1). Baseline characteristics are shown in Table 1. There were no significant differences in baseline demographic and laboratory findings between the IC morphine and control groups. The median age of the total patients was 60 years (49.5–66.5 years). More than 80% of patients were male in both groups. There was no significant difference in use of P2Y₁₂ receptor inhibitor (ticagrelor or clopidogrel). Angiographic and procedural findings were well balanced between the groups as well. Forty-two patients (52.5%) had 1-vessel disease, and the left anterior descending artery was the most commonly involved coronary artery. Most patients underwent stent implantation in the culprit coronary artery.

Cardiac Magnetic Resonance Results

There was no significant difference in the intervals from PCI to CMR between the 2 groups (3 [3–4] days for both groups, $P=0.88$). CMR data are shown in Table 2. LV mass was significantly smaller in the control group, but both primary and secondary outcomes did not show any differences between the groups. The primary outcome, myocardial infarct size, was similar ($25.6 \pm 11.2\%$ vs $24.6 \pm 10.5\%$, $P=0.77$) between the 2 groups, as were other CMR parameters including MVO extent and myocardial salvage index (Figure 2). In subgroup analysis the neutral effect of IC morphine was consistent among the various subgroups, but there was significant interaction between the treatment effect of IC morphine during primary PCI and prior use of morphine. IC morphine tended to decrease infarct size in patients receiving morphine before randomization (Figure 3).

Angiographic, ECG, Biochemical, and Clinical Outcomes

Angiographic, ECG, and biochemical outcomes are displayed in Table 3. All but 1 patient achieved final TIMI flow grade of 3, and the prevalence of postprocedural myocardial blush grade 2 to 3 was similar in both groups. The frequency of complete ST-segment resolution 30 minutes after PCI and peak CK-MB levels were not different between the 2 groups. In-hospital complications and pharmacologic therapy did not show differences between the IC morphine and the control group (Tables S1 and S2). During the 6-month follow-up, only 1 patient in the IC morphine group was admitted for heart failure management.

Discussion

In this prospective randomized study we investigated whether IC morphine administration could reduce the size of myocardial infarction in STEMI patients undergoing primary PCI. The major finding of this study was that IC morphine administration could not reduce myocardial infarct size evaluated by CMR compared with the control group. There were no differences in myocardial salvage index or the extent of MVO between the 2 groups either. Other estimates of myocardial injury including ST-segment resolution and a peak CK-MB level showed no difference between groups. Exploratory subgroup analyses showed consistent neutral effects of morphine in various subgroups. To our knowledge, this is the first prospective randomized study to evaluate the

Table 1. Baseline Characteristics

	IC Morphine (n=42)	Control (n=38)	P Value
Age, y	57.5 (49.0-66.0)	62.0 (50.0-67.0)	0.42
Male	37 (88.1)	31 (81.6)	0.54
Height, cm	168.0 (162.0-173.0)	167.5 (164.0-171.0)	0.43
Weight, kg	69.2 (63.9-76.2)	67.4 (59.3-72.3)	0.26
Hypertension	17 (40.5)	14 (36.8)	0.82
Diabetes mellitus	10 (23.8)	9 (23.7)	>0.999
Dyslipidemia	11 (26.2)	10 (26.3)	>0.999
Smoking	33 (78.6)	28 (73.7)	0.79
History of CVA	4 (9.5)	0 (0)	0.12
Platelet count, $\times 10^6$	233 (205-270)	221 (191-249)	0.19
Total cholesterol, mg/dL	201 (183-230)	193 (169-216)	0.24
LDL, mg/dL	137.5 (117.0-161.0)	117.0 (104.5-142.5)	0.06
Serum creatinine, mg/dL	0.98 (0.83-1.07)	0.90 (0.79-1.05)	0.18
Initial glucose, mg/dL	157 (137-179)	141 (123-173)	0.16
Hs-CRP, mg/dL	0.11 (0.04-0.29)	0.08 (0.05-0.18)	0.93
Symptom to balloon time, minutes	167 (112-283)	158 (108-243)	0.78
Door to balloon time, minutes	67 (53-76)	69 (51-78)	0.64
Culprit vessel			
LAD	23 (54.8)	21 (55.3)	>0.999
LCX	3 (7.1)	3 (7.9)	>0.999
RCA	16 (38.1)	14 (36.8)	>0.999
Number of diseased vessels			
1	22 (52.4)	20 (52.6)	>0.999
2	14 (33.3)	15 (39.5)	0.64
3	6 (14.3)	3 (7.9)	0.49
Lesion type B2/C	38 (90.5)	36 (94.7)	0.68
Initial TIMI flow grade			
0	38 (90.5)	37 (97.4)	0.36
1	4 (9.5)	1 (2.6)	
Thrombus aspiration	27 (64.3)	25 (65.8)	>0.999
Stent insertion	42 (100)	36 (94.7)	0.22
Stent diameter, mm	3.0 (2.75-3.5)	3.0 (2.75-3.5)	0.91
Stent length, mm	28 (23-30)	27 (19-33)	0.33
P2Y ₁₂ receptor inhibitor			
Clopidogrel	25 (59.5)	20 (52.6)	0.65
Ticagrelor	17 (40.5)	18 (47.4)	
Glycoprotein IIb/IIIa inhibitors	4 (9.5)	3 (7.9)	>0.999

Values are reported as median (25th-75th percentiles) or n (%). CVA indicates cerebrovascular accident; Hs-CRP, high-sensitivity C-reactive protein; IC, intracoronary; LAD, left anterior descending; LCX, left circumflex; LDL, low-density lipoprotein; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

cardioprotective effect of IC morphine in STEMI patients undergoing primary PCI using CMR.

Primary PCI has been shown to be an effective reperfusion therapy for STEMI to restore coronary artery blood flow and

has contributed to reducing mortality of STEMI.¹ However, abrupt reperfusion after prolonged coronary occlusion can induce myocardial and vascular injury. The beneficial effects of primary PCI are limited by reperfusion injury, and lethal

Table 2. CMR Findings

	IC Morphine (n=42)	Control (n=38)	P Value
LV end-diastolic volume, mL	143.7±31.0	139.9±28.7	0.57
LV end-systolic volume, mL	67.6±25.6	67.2±20.9	0.90
LV ejection fraction, %	53.9±10.0	52.4±7.8	0.42
LV mass, mL	116.2±27.7	104.7±23.5	0.04
Infarct size (%LV)	25.6±11.2	24.6±10.5	0.77
Area at risk (%LV)	35.7±11.9	34.4±13.2	0.59
Myocardial salvage index, %	31.1±15.2	30.3±10.9	0.75
Extent of MVO (%LV)	6.0±6.3	5.1±4.6	0.91
Mean transmural score	2.1±0.4	2.0±0.4	0.31
Number of segments with transmural infarction ≥75%	3 (2-6)	4 (2-6)	0.86

Values are reported as mean±SD or median (25th-75th percentiles). CMR indicates cardiac magnetic resonance; intracoronary; LV, left ventricle; MVO, microvascular obstruction.

reperfusion injury is reported to account for up to 50% of the final size of a myocardial infarct.¹⁹ Although several cardioprotective strategies have been attempted to prevent reperfusion injury and to reduce myocardial infarct size, none of them has been definitively proven to be effective.^{10,20-22} Considering the high mortality and substantial rate of patients with LV dysfunction after STEMI, identifying an effective therapy for preventing lethal reperfusion injury is highly demanding. Therefore, we conducted the present trial to investigate the beneficial effects of IC morphine on myocardial infarct size in patients undergoing primary PCI.

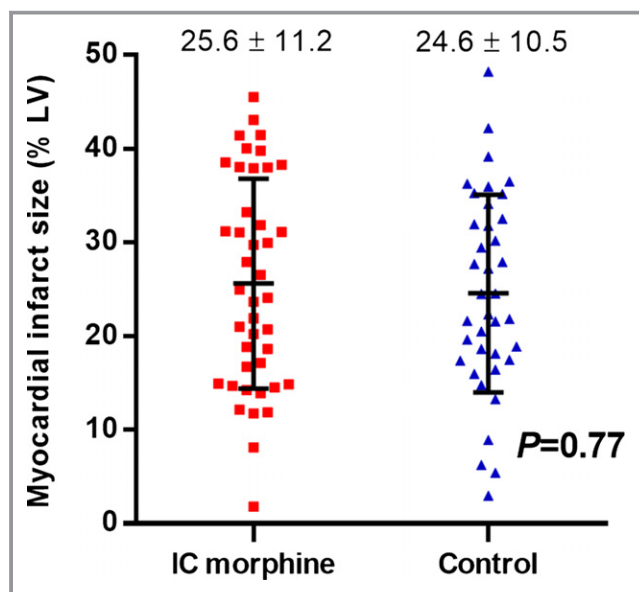


Figure 2. Myocardial infarct size in the intracoronary morphine and saline group. IC indicates intracoronary; LV, left ventricle.

Morphine has been used to control nitrate-unresponsive chest pain in acute myocardial infarction.^{16,23} Apart from its analgesic effects, morphine can also lower myocardial oxygen demand by reducing sympathetic activation and dilating peripheral vessels.²⁴ Moreover, previous laboratory and animal data reported a protective effect of morphine and its derivatives for prevention of reperfusion injury. Additionally, a cardioprotective role of morphine via opioid receptors has been demonstrated, and previous studies have reported that morphine can reduce reperfusion injury and infarct size of the myocardium in a way similar to that of ischemic preconditioning.^{10,25} One previous clinical trial showed that remote ischemic preconditioning and morphine infusion played a preventive role in reperfusion injury of STEMI patients.²⁵ It compared the efficacy of 3 treatment groups: control, remote ischemic preconditioning alone, or remote ischemic preconditioning plus morphine infusion. The last group showed the best efficacy, and the authors suggested a potential role of opioid action in ischemic postconditioning. Thus, we conducted a prospective, randomized trial on STEMI patients and analyzed myocardial infarct size using CMR images to investigate the cardioprotective role of morphine more accurately and directly. We administered morphine into the coronary artery expecting superior efficacy based on recent studies implying improved results with intracoronary injection of cardioactive drugs compared with intravenous application.¹¹⁻¹³

In our present study we demonstrated that IC morphine during primary PCI did not reduce myocardial infarct size, but there is a possibility that our findings resulted from study design rather than lack of actual morphine benefit. First, morphine could not reach the infarcted myocardium due to impaired coronary flow. However, we injected morphine into the coronary artery immediately after restoration of blood flow. In some patients morphine was administered locally at the site of the infarct lesion via thrombus aspiration catheter instead of via guiding catheter only, but subgroup analysis showed no significant difference in treatment effect of IC morphine according to method of administration. Local concentrations of morphine might be much higher with IC administration than with intravenous administration regardless of the use of thrombus aspiration catheter. Second, whether the dose of morphine was adequate is uncertain. Due to lack of data, we arbitrarily chose 3 mg of morphine sulfate, which was a little bit smaller than the conventional intravenous dose. Third, some patients received intravenous morphine at the emergency room for pain control. We did not exclude those receiving morphine before randomization because pain control is 1 of the important treatment goals in patients with STEMI, and the use of morphine is frequently inevitable in real-world practice. Subgroup analysis showed a significant interaction between the treatment effect of IC

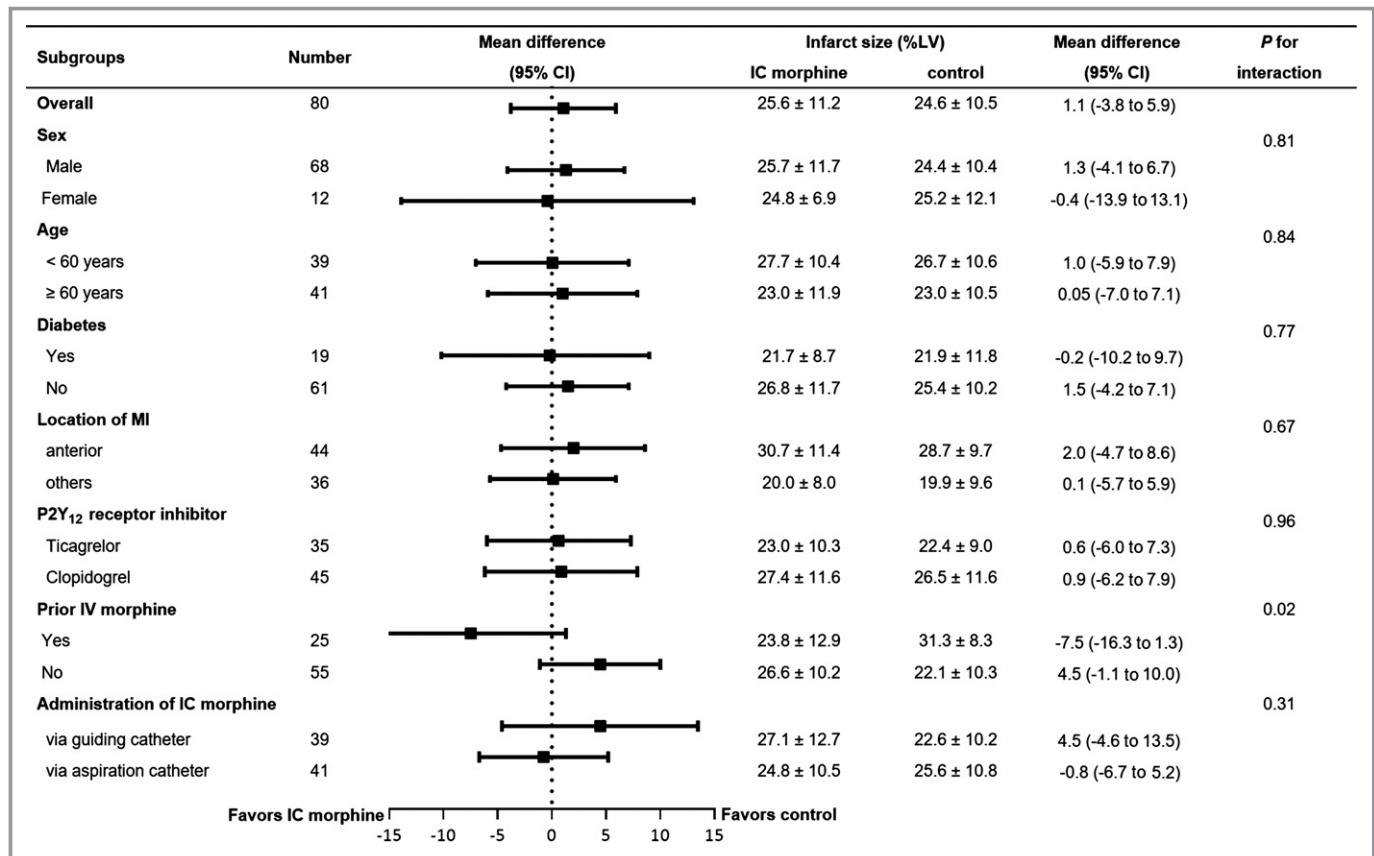


Figure 3. Forest plot subgroup analyses for myocardial infarct size. CI indicates confidence interval; IC, intracoronary; IV, intravenous; LV, left ventricle; MI, myocardial infarction.

Table 3. Angiographic, ECG, and Biochemical Outcomes

	IC Morphine (n=42)	Control (n=38)	P Value
Final TIMI flow grade			>0.999
2	1 (2.4)	0 (0)	
3	41 (97.6)	38 (100)	
Myocardial blush grade			>0.999
0/1	9 (21.4)	9 (23.7)	
2	13 (31.0)	12 (31.6)	
3	20 (47.6)	17 (44.7)	
Complete ST resolution at 30 minutes	16 (38.1)	14 (36.8)	>0.999
Complete ST resolution at 60 minutes	18 (42.9)	21 (55.3)	0.37
Peak CK-MB, ng/mL	231 (133.6-307.0)	234.9 (110.1-288.7)	0.54

Values are reported as median (25th-75th percentiles) or n (%). CK-MB indicates creatine kinase-myocardial band fraction; ECG, electrocardiogram; IC, intracoronary; TIMI, thrombolysis in myocardial infarction.

morphine during primary PCI and prior use of morphine. Prior use of morphine per se might have protective effects on myocardial infarct size, or the accumulated dose might reach therapeutic concentration. However, these findings should be interpreted with caution and are hypothesis generating at best. We cannot exclude a possibility of play of chance.

The potential beneficial effects of morphine might be negated by a pleomorphic effect that counterbalances its cardioprotective effect. Several pharmacokinetic and pharmacodynamic studies have proposed adverse effects of morphine in association with delayed activity of P2Y₁₂ receptor inhibitors by its delaying absorption in the gastrointestinal tract.^{26,27} A recent study reported adverse effects of morphine in terms of larger infarct size, higher extent of MVO, and lower myocardial salvage index.²⁸ However, morphine did not show any harmful effects in our study. Taken together, it seems to be unlikely that morphine administration during primary PCI is protective in patients undergoing primary PCI under current standard practices. Our primary end point of infarct size measured by CMR is a widely accepted gold standard for myocardial damage and is significantly correlated with long-term clinical outcomes in patients with STEMI.²⁹ However, because morphine delays absorption of P2Y₁₂

receptor inhibitors, a large study is needed to investigate the consequence of reduced inhibition of platelet activation by morphine administration.

Study Limitations

There are some limitations of the current study. First, all study drugs were open label, but primary outcome measurement was blinded. Second, there is a chance of selection bias because CMR analysis was not available for all randomized patients. However, this study is comparable to other studies in the acquisition rate of CMR (87.9%).^{30,31} Third, the primary outcome of our study was measured at a relatively early phase after STEMI, and only 6-month clinical outcomes were evaluated. Assessment of long-term results regarding ventricular remodeling after infarct maturation and long-term clinical events is still needed.

Conclusions

In this prospective randomized trial, IC morphine could not reduce myocardial infarct size compared with the control in STEMI patients undergoing primary PCI. However, it may be worthwhile to investigate whether different dose, timing, or route of administration of morphine would reduce myocardial infarct size.

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Disclosures

None.

References

- Pedersen F, Butrymovich V, Kelbaek H, Wachtell K, Helqvist S, Kastrup J, Holmvang L, Clemmensen P, Engstrom T, Grande P, Saunamaki K, Jorgensen E. Short- and long-term cause of death in patients treated with primary PCI for STEMI. *J Am Coll Cardiol*. 2014;64:2101–2108.
- Weir RA, McMurray JJ, Velazquez EJ. Epidemiology of heart failure and left ventricular systolic dysfunction after acute myocardial infarction: prevalence, clinical characteristics, and prognostic importance. *Am J Cardiol*. 2006;97:13F–25F.
- Poli A, Fèveau R, Vandoni P, del Rosso G, D'Urbano M, Seveso G, Cafiero F, De Servi S. Integrated analysis of myocardial blush and ST-segment elevation recovery after successful primary angioplasty: real-time grading of microvascular reperfusion and prediction of early and late recovery of left ventricular function. *Circulation*. 2002;106:313–318.
- Stone GW, Peterson MA, Lansky AJ, Dangas G, Mehran R, Leon MB. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. *J Am Coll Cardiol*. 2002;39:591–597.
- Garcia-Dorado D, Piper HM. Postconditioning: reperfusion of "reperfusion injury" after hibernation. *Cardiovasc Res*. 2006;69:1–3.
- Piper HM, Garcia-Dorado D, Ovize M. A fresh look at reperfusion injury. *Cardiovasc Res*. 1998;38:291–300.
- Garcia-Dorado D, Rodriguez-Sinovas A, Ruiz-Meana M, Inserte J. Protection against myocardial ischemia-reperfusion injury in clinical practice. *Rev Esp Cardiol (Engl Ed)*. 2014;67:394–404.
- Gross ER, Hsu AK, Gross GJ. Opioid-induced cardioprotection occurs via glycogen synthase kinase β inhibition during reperfusion in intact rat hearts. *Circ Res*. 2004;94:960–966.
- Obame FN, Plin-Mercier C, Assaly R, Zini R, Dubois-Randé JL, Berdeaux A, Morin D. Cardioprotective effect of morphine and a blocker of glycogen synthase kinase β , SB216763 [3-(2,4-dichlorophenyl)-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione], via inhibition of the mitochondrial permeability transition pore. *J Pharmacol Exp Ther*. 2008;326:252–258.
- Forster K, Kuno A, Solenkova N, Felix SB, Krieg T. The δ -opioid receptor agonist DADLE at reperfusion protects the heart through activation of pro-survival kinases via EGF receptor transactivation. *Am J Physiol Heart Circ Physiol*. 2007;293:H1604–H1608.
- Wohrle J, Grebe OC, Nusser T, Al-Khayer E, Schaible S, Kochs M, Hombach V, Hoher M. Reduction of major adverse cardiac events with intracoronary compared with intravenous bolus application of abciximab in patients with acute myocardial infarction or unstable angina undergoing coronary angioplasty. *Circulation*. 2003;107:1840–1843.
- Lee CH, Low A, Tai BC, Co M, Chan MY, Lim J, Lim YT, Tan HC. Pretreatment with intracoronary adenosine reduces the incidence of myonecrosis after non-urgent percutaneous coronary intervention: a prospective randomized study. *Eur Heart J*. 2007;28:19–25.
- Thiele H, Schindler K, Friedenberger J, Eitel I, Fumagalli G, Grebe E, Erbs S, Linke A, Mobius-Winkler S, Kivelitz D, Schuler G. Intracoronary compared with intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: the randomized Leipzig immediate percutaneous coronary intervention abciximab IV versus IC in ST-elevation myocardial infarction trial. *Circulation*. 2008;118:49–57.
- Hahn JY, Song YB, Kim EK, Yu CW, Bae JW, Chung WY, Choi SH, Choi JH, Bae JH, An KJ, Park JS, Oh JH, Kim SW, Hwang JY, Ryu JK, Park HS, Lim DS, Gwon HC. Ischemic postconditioning during primary percutaneous coronary intervention: the effects of postconditioning on myocardial reperfusion in patients with ST-segment elevation myocardial infarction (POST) randomized trial. *Circulation*. 2013;128:1889–1896.
- Kim EK, Choi JH, Song YB, Hahn JY, Chang SA, Park SJ, Lee SC, Choi SH, Choe YH, Park SW, Gwon HC. A protective role of early collateral blood flow in patients with ST-segment elevation myocardial infarction. *Am Heart J*. 2016;171:56–63.
- O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362–e425.
- Song YB, Hahn JY, Gwon HC, Kim JH, Lee SY, Choe YH, Choi SH, Choi JH, Lee SH. Upstream high-dose tirofiban does not reduce myocardial infarct size in patients undergoing primary percutaneous coronary intervention: a magnetic resonance imaging pilot study. *Clin Cardiol*. 2009;32:321–326.
- Ortiz-Perez JT, Lee DC, Meyers SN, Davidson CJ, Bonow RO, Wu E. Determinants of myocardial salvage during acute myocardial infarction: evaluation with a combined angiographic and CMR myocardial salvage index. *JACC Cardiovasc Imaging*. 2010;3:491–500.
- Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med*. 2007;357:1121–1135.
- Kim SJ, Kim W, Woo JS, Ha SJ, Kang WY, Hwang SH, Kang DG, Lee SU, Cho SK, Im JS, Kim W. Effect of myocardial protection of intracoronary adenosine and nicorandil injection in patients undergoing non-urgent percutaneous coronary intervention: a randomized controlled trial. *Int J Cardiol*. 2012;158:88–92.
- Selker HP, Beshansky JR, Sheehan PR, Massaro JM, Griffith JL, D'Agostino RB, Ruthazer R, Atkins JM, Sayah AJ, Levy MK, Richards ME, Aufderheide TP, Braude DA, Pirrallo RG, Doyle DD, Frascione RJ, Kosiak DJ, Leaming JM, Van Gelder CM, Walter GP, Wayne MA, Woolard RH, Opie LH, Rackley CE, Apstein CS, Udelson JE. Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial. *JAMA*. 2012;307:1925–1933.
- Yang XM, Liu Y, Cui L, Yang X, Liu Y, Tandon N, Kambayashi J, Downey JM, Cohen MV. Platelet P2Y₁(2) blockers confer direct postconditioning-like protection in reperfused rabbit hearts. *J Cardiovasc Pharmacol Ther*. 2013;18:251–262.
- Task Force on the management of ST segment elevation acute myocardial infarction of the European Society of Cardiology, Steg PG, James SK, Atar D,

- Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569–2619.
24. Rouby JJ, Eurin B, Glaser P, Guillochon JJ, Nafziger J, Guesde R, Viars P. Hemodynamic and metabolic effects of morphine in the critically ill. *Circulation*. 1981;64:53–59.
 25. Rentoukas I, Giannopoulos G, Kaoukis A, Kossyvakis C, Raisakis K, Driva M, Panagopoulou V, Tsarouchas K, Vavetsi S, Pyrgakis V, Deftereos S. Cardio-protective role of remote ischemic preconditioning in primary percutaneous coronary intervention: enhancement by opioid action. *JACC Cardiovasc Interv*. 2010;3:49–55.
 26. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, Stankowska K, Buszko K, Navarese EP, Jilma B, Siller-Matula JM, Marszall MP, Rosc D, Kozinski M. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J*. 2016;37:245–252.
 27. Parodi G, Bellandi B, Xanthopoulou I, Capranzano P, Capodanno D, Valenti R, Stavrou K, Migliorini A, Antoniucci D, Tamburino C, Alexopoulos D. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2015;8:e001593.
 28. de Waha S, Eitel I, Desch S, Fuernau G, Lurz P, Urban D, Schuler G, Thiele H. Intravenous morphine administration and reperfusion success in ST-elevation myocardial infarction: insights from cardiac magnetic resonance imaging. *Clin Res Cardiol*. 2015;104:727–734.
 29. Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger CB, Jenkins PL, Nichols M, Ben-Yehuda O. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. *J Am Coll Cardiol*. 2016;67:1674–1683.
 30. Stone GW, Maehara A, Witzenbichler B, Godlewski J, Parise H, Dambrink JH, Ochala A, Carlton TW, Cristea E, Wolff SD, Brener SJ, Chowdhary S, El-Omar M, Neunteufl T, Metzger DC, Karwoski T, Dizon JM, Mehran R, Gibson CM; INFUSE-AMI Investigators. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA*. 2012;307:1817–1826.
 31. Patel MR, Smalling RW, Thiele H, Barnhart HX, Zhou Y, Chandra P, Chew D, Cohen M, French J, Perera D, Ohman EM. Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial. *JAMA*. 2011;306:1329–1337.

SUPPLEMENTAL MATERIAL

Table S1. In-hospital complications

	IC morphine (n=42)	Control (n=38)	<i>P</i> value
Death	0 (0)	0 (0)	N/A
Intra-aortic balloon pump	1 (2.4)	1 (2.6)	>0.999
Acute pulmonary edema	0 (0)	1 (2.6)	0.48
Bleeding	0 (0)	1 (2.6)	0.48
Recurrent ischemia	0 (0)	0 (0)	N/A
Arrhythmia	1 (2.4)	2 (5.3)	0.60
Stroke	0 (0)	1 (2.6)	0.48
Infection	1 (2.4)	1 (2.6)	>0.999

Values are reported as n (%). IC indicates intracoronary; N/A, not applicable.

Table S2. Pharmacology therapy

	IC morphine (n=42)	Control (n=38)	<i>P</i> value
Aspirin	100 (100)	100 (100)	N/A
P2Y12 receptor inhibitor	100 (100)	100 (100)	N/A
Statins	100 (100)	100 (100)	N/A
Beta blockers	38 (90.5)	34 (89.5)	>0.999
Renin-angiotensin system blocker	35 (83.3)	35 (92.1)	0.32

Values are reported as n (%). IC indicates intracoronary; N/A, not applicable.