This article can be cited as: Hashemzadeh F, Ghafouri-Asbagh A, Khalaji A, et al. The impact of using morphine or meperidine on clinical outcomes of ST-elevation myocardial infarction patients undergoing primary percutaneous intervention. Cardiovasc Biomed J. 2025;5(2): 51-58.

Original Article

The impact of using morphine or meperidine on clinical outcomes of ST-elevation myocardial infarction patients undergoing primary percutaneous intervention

Farzaneh Hashemzadeh [1], ***Amirhosein Ghafouri-Asbagh*** [1], ***Amirreza Khalaji*** [2], ***Negar Jafari*** [1], ***Ahmad Separham*** [1,*]

[1] Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Immunology Research Center, Tabriz University of medical sciences, Tabriz, Iran

*** Corresponding Author:**
Address: Tabriz, Vali Asr St., No. 8, West Razi St., Third Floor, Tabriz, Iran. **Postal code:** 5166614766; **Tel:** +98 4133373741; **Email:** aseparham@gmail.com

Article Information:
Received: 06 Aug 2025; Revised: 09 Oct 2025; Accepted: 22 Dec 2025 DOI: 10.18502/cbj.v5i2.21136

Abstract

Objectives: Opioids are commonly used for treating chest pain in patients with acute coronary syndrome. Despite the beneficial effects of opioids, they could have adverse effects on patients, too. This study aims to compare the effects of morphine and meperidine on major adverse cardiac events (MACE) and mortality in patients undergoing percutaneous intervention.

Methods: The researchers retrospectively reviewed data from 161 patients with the confirmed diagnosis of ST-elevation myocardial infarction undergoing primary percutaneous intervention. We compared the medical records of patients with MACE. In-hospital and one-year MACE were our primary measured outcomes.

Results: Patients treated with morphine were more likely to experience in-hospital MACE (P-value: 0.006). Heart failure in the hospital was more in the morphine group (p-value: 0.002). However, none of the one-year clinical outcomes were statistically different between the two groups treated with morphine or meperidine. Left ventricular ejection fraction, ischemic heart disease, and hospital length of stay remained independent variables for predicting both in-hospital and one-year MACE, but morphine or meperidine didn't remain independent in multivariable analysis.

Conclusions: Although heart failure occurred more frequently in patients who received morphine, neither morphine nor meperidine independently predicted in-hospital or one-year MACE.

Keywords: ST-elevation MI, Percutaneous intervention, Morphine, Meperidine

Introduction

ST-segment elevation myocardial infarction (STEMI) is characterized by electrocardiographic (ECG) findings of new left bundle branch block or in two continuous leads new ST-segment elevations, the finding of biomarkers that are indicative of myocardial injury, and myocardial ischemic symptoms (1). Providentially, the mortality rate of coronary heart disease has declined due to advances in treatment (2). The dominant reperfusion method has been Primary percutaneous coronary intervention (pPCI) in STEMI for over a decade (3). The use of opioids has remained a significant component of analgesia in managing STEMIs in the emergent situation. As a

result of its analgesic properties, it provides symptomatic relief. Moreover, the reduction of pain may lead to a decrease in physiological sympathetic activity, which in turn decreases systemic blood pressure and heart rate, resulting in a physiological adjustment (4). Even though opioids and morphine are commonly used in daily practice in patients with STEMI, clinical research in the past few years has shown the adverse effects of opioids on these patients (5).The first line agent commonly used to treat MI chest pain is morphine. However, morphine can lead to various adverse effects in treating these patients (6). In addition to morphine, meperidine is another opioid that can be used in treating STEMI. Patients with ischemic chest pain respond similarly to meperidine as far as efficacy and safety are concerned. The side effects of meperidine are similar to those of morphine, including respiratory depression, vomiting, and nausea (7). The most common treatment for STEMI chest pain is treatment with morphine and meperidine (8). Although morphine remains the most frequently used opioid for chest pain in STEMI, concerns have been raised regarding its potential effects on myocardial reperfusion outcomes. Meperidine is also occasionally used for analgesia in this context, but clinical evidence regarding its safety and efficacy in STEMI patients is minimal. Therefore, we performed this retrospective study to evaluate and compare the impact of morphine and meperidine on in-hospital and one-year MACE in STEMI patients undergoing pPCI.

Materials and Methods

This retrospective study was conducted from March 2018 to March 2020. The participants included all patients with a confirmed diagnosis of STEMI who underwent primary percutaneous intervention. This study is in accordance with the Helsinki declaration. The Ethics Committee approved the study protocol (Registration Code: IR.TBZMED.REC.1399.117). The study was retrospective; therefore, no consent forms were required. The hospital medical records provided the patient's data. The presence of ST-segment elevation of more than 2.5 mm in males under 40, more than 2 mm in males over 40, or more than 1.5 mm in females in leads V2-V3, and more than 1 mm in other leads was the criterion for diagnosing STEMI [1]. Inclusion criteria included adults diagnosed with STEMI based on electrocardiographic criteria and cardiac biomarkers, patients who underwent primary pPCI, and administration of either morphine or meperidine for pain control. According to hospital protocols, intravenous morphine was administered at 5 mg boluses, adjusted according to the patient's pain relief needs. Meperidine was administered intravenously at 50 mg. The choice of analgesic was at the discretion of the treating cardiologist, based on clinical judgment. Exclusion criteria included patients who received thrombolytic therapy, incomplete or missing medical records, patients who required emergency surgery after angiography, the presence of severe valvular heart disease, and a history of heart failure. Finally, the researchers selected 161 patients. The data were collected in a prepared checklist, and two investigators independently reviewed the records; discrepancies were resolved by consensus. These included demographic variables such as age, sex, status of smoking, vital signs, and comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, and history of previous cardiovascular diseases. Additionally, angiographic, echocardiographic, and laboratory findings based on routine blood tests were collected. Patients were classified into two groups based on the occurrence of adverse cardiovascular events (MACE) during their hospitalization, allowing for a comparison of medical records between the two groups. In-hospital MACE was defined as a composite of several parameters, including mortality during the hospital stay, heart failure, new myocardial infarction (MI), and bleeding. One-year MACE consisted of mortality during follow-up, heart failure, further MI, and rehospitalization due to cardiac complications. The primary objective of this study was to compare the effects of morphine and meperidine on both in-hospital and one-year major adverse cardiovascular events (MACE) in patients with ST-Elevation Myocardial Infarction (STEMI) who underwent primary percutaneous coronary intervention. Statistical analyses were performed using SPSS Version 21.0 (IBM SPSS Corporation, Chicago, IL). To assess the normality of the data, the Kolmogorov-Smirnov test was utilized for continuous variables. Qualitative data were presented as frequencies and percentages (%). Quantitative data were expressed as means with standard deviations (SD) for normally distributed data and as medians with interquartile ranges for nonparametric data. For normally distributed continuous variables, an independent samples t-test was employed. A Mann-Whitney U test was used for nonparametric data. Categorical variables were analyzed using either Fisher's exact test or the chi-square test. Multivariable analysis was conducted for variables with a P-value of less than 0.05 in univariable analysis. Odds ratios

(OR) and confidence intervals (CI) were calculated to identify independent predictors of MACE. Statistical significance was defined as a P-value of less than 0.05. And as median (interquartile range) when nonparametric tests were used. For normally distributed continuous variables, an independent samples t-test is used, and for nonparametric data, a Mann-Whitney U test is used. The Fisher's exact test or the chi-square test, as appropriate, was used to analyze categorical variables. Multivariable analysis was applied to variables having a P-value of less than 0.05 in univariable analysis. The odds ratio (OR) and confidence intervals (CI) were calculated to establish the independent predictors of MACE. Statistical significance was defined as a P value of less than 0.05.

Results

A total of 161 patients with a mean age of 59.96 ± 9.98 years participated in this retrospective study. Table 1 shows the clinical information and baseline characteristics of the patients.

Table 1. Laboratory and paraclinical findings in whole patients and patients with and without in-hospital MACE

	Total (n=161)	With MACE (n=104)	Without MACE (n=57)	P-value
Age mean ± SD	59.96 ± 9.98	59.59 ± 9.69	60.64 ± 10.55	0.524
Males n, (%)	143 (88.8)	91 (63.6)	52 (36.4)	0.604
HB (g/dl)	14.41 ± 2.27	14.15 ± 2.40	14.95 ± 1.88	0.081
PLT (10^3 counts/nl)	222.88 ± 66.14	228.58 ± 69.15	207.22 ± 55.61	0.152
Cr	1.31 ± 0.75	1.35 ± 0.86	1.20 ± 0.35	0.300
O_2 saturation	96.06 ± 7.25	96.28 ± 8.92	95.66 ± 1.93	0.605
HR	83.81 ± 16.59	86.15 ± 16.70	79.56 ± 15.67	0.015
SBP	137.42 ± 24.54	136.43 ± 25.90	139.22 ± 21.97	0.491
DBP	84.83 ± 14.80	85.04 ± 14.90	84.45 ± 14.74	0.809
LVEF	34.39 ± 7.13	30.98 ± 6.05	40.61 ± 4.10	<0.001
LVEF < 40%	104 (64.6)	91 (87.5)	13 (12.5)	<0.001
Smoking	91 (56.5)	58 (63.7)	33 (36.3)	0.463
DM	54 (33.5)	31 (57.4)	23 (42.6)	0.119
HTN	83 (51.6)	57 (68.7)	26 (31.3)	0.171
FH	23 (14.3)	11 (47.8)	12 (52.2)	0.059
HLP	29 (18.0)	17 (58.6)	12 (41.4)	0.295
Prior CABG	2 (1.2)	2 (100.0)	0 (0.0)	0.416
Prior PCI	17 (10.6)	13 (76.5)	4 (23.5)	0.210
Prior IHD	24 (14.9)	21 (87.5)	3 (12.5)	0.008
Hospital LOS	6.16 ± 3.97	6.80 ± 4.63	4.98 ± 1.84	0.005
Anterolateral MI	102 (63.4)	82 (80.4)	20 (19.6)	<0.001
DBT(min)	85.13 ± 34.54	86.73 ± 37.73	82.01 ± 27.39	0.421
Culprit				
LAD	98 (60.9)	78 (79.6)	20 (20.4)	0.052
LCX	22 (13.7)	11 (50.0)	11 (50.0)	
RCA	37 (23.0)	12 (32.4)	25 (67.6)	
LAD-LCX	2 (1.2)	2 (100.0)	0 (0.0)	
LAD-RCA	1 (0.6)	1 (100.0)	0 (0.0)	
LCX-RCA	1 (0.6)	0 (0.0)	1 (100.0)	
STR	62.67 ± 24.78	57.47 ± 25.88	72.17 ± 19.48	<0.001
STR > 50	101 (62.7)	57 (56.4)	44 (43.6)	0.004
1 vessel disease	80 (49.6)	48 (60.0)	32 (40.0)	0.082
2 vessel disease	42 (26.4)	25 (59.5)	17 (40.5)	
3 vessel disease	37 (22.8)	29 (78.4)	8 (21.6)	
Stent				
Drug-eluting stent	148 (93.7)	97 (65.5)	51 (34.5)	0.681
Bare metal stent	8 (5.1)	5 (62.5)	3 (37.5)	
Both	2 (1.3)	1 (50.0)	1 (50.0)	
GpIIb/IIIa inh.	140 (87.0)	87 (62.1)	53 (37.9)	0.072

	Total (n=161)	With MACE (n=104)	Without MACE (n=57)	P-value
Peak CTNI	26.37 ± 20.11	28.00 ± 21.41	23.18 ± 17.07	0.208
Morphine	115 (71.4)	82 (71.3)	33 (28.7)	0.006
Meperidine	46 (28.6)	22 (47.8)	24 (52.2)	0.006

Only 18 (11.2%) women participated in our study population, whereas men made up almost 90% of the participants. The mean (SD) time from door to balloon (DBT) was 85.13 ± 34.54 minutes for the entire population. Patients with in-hospital Major adverse cardiovascular events (MACE) had a longer DBT, but this difference was not statistically significant (p-value: 0.421). The average length of stay in the hospital was 6.16 ± 3.97 days, and those who had an in-hospital MACE had a longer time of hospitalization (6.80 ± 4.63 vs. 4.98 ± 1.84, p-value: 0.005). Additionally, the MACE-positive group had a higher mean heart rate (86.15 ± 16.70 vs. 79.56 ± 15.67, p-value = 0.015). LVEF was less than 40% in more than 60% of the patients. The majority of them were in the MACE-positive group (p-value = 0.001). The three most prevalent comorbidities in the study population were hypertension (51.6%), diabetes mellitus (33.5%), and hyperlipidemia (18.0%), and more than half of the patients were smokers. Only about 10% of the 24 (14.9%) patients with prior ischemic heart disease did not have an in-hospital MACE (p-value: 0.008). Anterolateral MI was observed in 102 patients (63.4%) and was more prevalent in the MACE-positive group (p-value = 0.001). In our study population, the LAD (60.9%), RCA (23.0%), and LCX (13.7%) were the three most common culprit lesions. The one-vessel disease affected nearly 50% of the patients, whereas two-vessel disease and three-vessel disease affected 26.8% and 22.4% of them, respectively. The mean ST-segment elevation resolution was 62.67 ± 24.78 and higher in the MACE negative group (57.47 ± 25.88 vs. 72.17 ± 19.48, p-value < 0.001). In our study population, 101 (62.7%) patients had STR, more than 50%. Morphine was used in 115(71.4%) patients, and 82(71.3%) of them experienced MACE during their hospital stay (p-value: 0.006). Nearly 30% of the patients were treated with meperidine after the percutaneous intervention, and more than half did not experience MACE during hospitalization (p-value: 0.006). Table 2 shows in-hospital complications of the entire study group, as well as patients in the morphine or meperidine group.

Table 2. In-hospital clinical outcomes in morphine and meperidine groups

	Total (n=161)	Morphine (n=115)	Meperidine (n=46)	P-value
In-hospital death	5 (3.1)	3 (60.0)	2 (40.0)	0.443
Heart failure	97 (60.2)	78 (80.4)	19 (19.6)	0.002
Further MI	1 (0.6)	1 (100.0)	0 (0.0)	0.714
Bleeding	1 (0.6)	0 (0.0)	1 (100.0)	0.286
In-hospital MACE	104 (64.6)	82 (78.8)	22 (21.2)	0.005

MACE: Major adverse cardiovascular events

The most common complication among the patients was heart failure (60.2%), more in the morphine group (p-value: 0.002). In-hospital mortality occurred in 5 (3.1%) patients, but there was no statistically difference between the two groups. In-hospital MACE was in 104 (64.6%) patients, and nearly 80% were in the morphine group (p-value: 0.005). Table 3 shows one-year clinical complications of the whole study population and the morphine and meperidine groups. Rehospitalization occurred in 12 (7.5%) patients, and 10 (6.2%) patients died within one year of follow-up. One-year MACE occurred in 28 (17.4%) patients, and none of the mentioned complications indicated a statistical difference between the two groups Table 3.

Table 3. One-year clinical outcomes in morphine and meperidine groups

	Total (n=161)	Morphine (n=115)	Meperidine (n=46)	P-value
One-year death	10 (6.2)	6 (60.0)	4 (40.0)	0.309
Heart failure	4 (2.5)	2 (50.0)	2 (50.0)	0.322
Further MI	2 (1.2)	2 (100.0)	0 (0.0)	0.509
Rehospitalization	12 (7.5)	7 (58.3)	5 (41.7)	0.233
One-year MACE	28 (17.4)	17 (60.7)	11 (39.3)	0.126

MACE: Major adverse cardiovascular events

Tables 4 and 5 present the results of a multivariable analysis, including HR, LVEF, history of IHD, and hospital length of stay, which remained independent risk factors for in-hospital MACE. (resp., P-value = 0.012; <0.001; 0.032; 0.027).

Table 4. Predictors of in-hospital MACE: multivariable analysis

	Odds ratio	95%CI	P-value
HR	1.048	1.010-1.087	0.012
LVEF	0.597	0.494-0.723	<0.001
IHD	13.806	1.593-119.609	0.032
Hospital LOS	1.298	1.030-1.697	0.027
Anterolateral MI	1.598	0.492-5.193	0.435
STR>50	0.481	0.159-1.461	0.197
Morphine	0.385	0.031-4.463	0.436
Meperidine	0.373	0.030-4.906	0.463

Table 5. Univariate and multivariate predictors of one year MACE

	Univariate OR(95%CI)	P-value	multivariate OR(95%CI)	P-value
HR	0.996 (0.971-1.021)	0.726		
LVEF	0.908 (0.856-0.964)	0.002	0.933 (0.876-0.994)	0.031
IHD	2.925 (1.106-7.773)	0.030	2.390 (0.841-6.787)	0.102
Hospital LOS	1.162 (1.052-1.284)	0.003	1.126 (1.016-1.246)	0.023
Anterolateral MI	1.926 (0.765-4.850)	0.164		
STR>50	0.631 (0.277-1.437)	0.272		
Morphine	0.552 (0.236-1.293)	0.171		
Meperidine	1.812 (0.774-4.243)	0.171		

CI: Confidence Interval

Moreover, multivariable analysis of one-year MACE predictors showed that only LVEF, IHD, and hospital length of stay remained independent variables. Morphine and meperidine did not remain independent in multivariable analysis for in-hospital or one-year MACE.

Discussion

This study is the first to directly compare morphine and meperidine in STEMI patients undergoing primary PCI. The findings indicate that morphine use is associated with higher rates of in-hospital MACE, mainly heart failure, while no differences were observed in one-year outcomes. The findings suggested that morphine and its active metabolites may lower plasma concentrations of P2Y12

inhibitors by reducing their gastrointestinal absorption (9). Opioid receptors are activated in the myenteric plexus and intestinal tract, which diminishes intestinal secretions and motility (10). In STEMI cases, blood shunting and activation of the sympathetic system to perfuse vital organs can delay absorption of P2Y12 inhibitors and exacerbate poor intestinal motility (11). Lower plasma levels of P2Y12 inhibitors with Morphine demonstrate no decrease in the antiplatelet effect, while research in cases with STEMI showed positive findings (9, 12). Additionally, the known intravenous morphine side effects, such as emesis and nausea, can affect the bioavailability of oral antiplatelet agents, which have poorer bioavailability in this setting (10). Though the correlation between oral antiplatelet actions, delayed onset, and morphine has been shown to persist, excluding subjects with vomiting suggests more mechanisms (12). In cases with STEMI, morphine, by decreasing heart rate and blood pressure, can reduce the demand for oxygen in the myocardium and then diminish the damage to the myocardium (6). Though in vital organs, Morphine may cause poor oxygen delivery by depressing respiratory drive. Also, Morphine has been demonstrated in some animal models to enhance the size of MI, while other research has shown a decrease in the size of infarct contributed by Morphine (13, 14). The STR is used to evaluate the effectiveness of myocardial reperfusion and its potential benefits to patients. In our study, the use of morphine in STEMI patients undergoing primary PCI was associated with a higher rate of in-hospital MACE, while meperidine showed no significant excess risk. These findings are consistent with previous reports suggesting that morphine may impair myocardial reperfusion and increase adverse short-term outcomes. In B. Bellandi et al.'s (15) study, morphine was associated with a higher rate of vomiting, poor STR, larger infarct sizes, and a tendency towards left ventricular dysfunction at discharge, which is in line with our study. Additionally, according to another study, mechanical reperfusion was less successful in patients who received Morphine and had a larger infarct size, a finding similar to ours (16). Fernando H et al. (17) investigated patients who were given morphine by emergency medical services before arriving at the hospital; there was a higher rise in cardiac biomarkers (troponin), which is similar to the results of the current study. On the other hand, another study has shown no difference between the patients who were given and those who were not given morphine in the increase of enzymes and length of hospitalization between patients, which is contrary to our study (18). Furthermore, Bonin et al. (19) showed no difference in the increase of cardiac biomarkers in the two groups who took Morphine and those who did not take Morphine in patients with anterior MI. Moreover, in another study, it was shown that there was no difference in infarct size in patients who underwent pPCI (20). The comparison between meperidine and Morphine showed that meperidine is safer because of its superiority in pain-associated renal colic or biliary spasm therapy. Nevertheless, some studies demonstrated that the meperidine benefits were nonexistent (21). Eisendrath et al. (22) revealed that the primary analgesic opioid in the USA is meperidine in clinical practice. On the other hand, data on meperidine in this context are scarce. However, older controlled studies have suggested comparable efficacy and tolerability to morphine, which aligns with our observation of no significant difference in one-year outcomes. In small studies, meperidine has been found to cause hemodynamic abnormalities in patients with acute myocardial infarction. According to Rees HA, meperidine caused more circulatory disturbances and unpleasant side effects in this small study than heroin. Despite this, several controlled clinical trials at that time comparing Morphine, nicomorphine, and meperidine trials of analgesic treatment in acute MI did not demonstrate that meperidine had severe side effects.As Nielsen et al. (7) demonstrated, Morphine, Nicomorphine, and meperidine are equally effective and well-tolerated in treating chest pain in patients suffering from acute MI. They also result in similar types of adverse reactions that are experienced by similar numbers of patients. An acute MI study was conducted by Lee et al. (23). Therapeutic doses of Morphine and meperidine did not have any deleterious hemodynamic effects. The limitations of this study include the small number of patients, the disproportionate percentage of men and women in the study, completing some patient files over the phone, the possibility of errors in recalling information, conducting the study retrospectively, not determining the size of the infarct, and the low rate of patients' mortality. In conclusion, this is the first study to compare the effect of Morphine and meperidine in STEMI patients who underwent pPCI. Neither morphine nor meperidine remains independent in predicting in-hospital or one-year MACE. But in this retrospective study, heart failure as an in-hospital complication occurred more frequently among STEMI patients who received

morphine. Despite all the benefits of opioids for pain control in patients, these medications can have adverse effects that change the outcome of our intervention. These results highlight the potential risks associated with opioid use in a single-center study. Also, our findings should be interpreted cautiously due to the retrospective design and limited sample size. Future large-scale, prospective studies are needed to confirm these associations and guide clinical practice.

Acknowledgments
We thank the staff of the Shahid Madani hospital for their cooperation who helped us gather the data used for this analysis.

Authors' contributions
Conceptualization and methodology: A.S, Data collection: F.H, Data analysis and interpretation: N.J, Drafting the article: A.GH, A.Kh, Revising and final approval of the manuscript: A.S. The manuscript has been read and approved by all the authors, and it is ensured that the requirements for authorship as stated earlier in this document have been met.

Conflicts of Interest
The authors declare that there is no conflict of interest.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical statement
This study is in accordance with Helsinki declaration and Ethics Committee approved the study protocol (Registration Code: IR.TBZMED.REC.1399.117), and we did not use informed consent since it was a retrospective study.

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