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# The Effect of Pain and Morphine Use on Complication Rates after Acute Myocardial Infarction

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## Abstract

**Background:** Patients with acute myocardial infarction usually presented to emergency department complaining from severe chest pain. This pain resulted from imbalance between oxygen supply and demand leading to serious complication. Different guidelines recommended the use of morphine as a drug of choice for this pain.

**Objective:** The purpose of this study was to check the effect of pain and morphine use on complication rate after acute myocardial infarction.

**Methods:** A cross-sectional design was used to meet the purpose of this study. Data were extracted from the medical records of 371 patients with diagnosis of acute myocardial infarction from four different hospitals in Amman, Jordan by trained cardiovascular research assistants.

**Results:** Patients with severe chest pain have more complications (1.65 ± 1.04 vs. 0.16 ± 1.14, $p < .001$) and longer length of stay in the intensive care units (5.98 ± 6.13 vs. 4.17 ± 6.99, $p < .05$) and in the hospital (7.34 ± 14.49 vs. 3.37 ± 3.04, $p < .001$) compared to patients with mild and moderate pain. The use of morphine did not have any protective effect against the development of complications or length of stay.

**Conclusion:** Pain increased complications and length of stay after acute myocardial infarction. Morphine use did not have a protective effect on these complications. Different treatment strategies (i.e. treating the cause) are highly recommended. Randomized control trials to check the effect of morphine use in patients with acute myocardial infarction is warranted

**Keywords:** Pain; Morphine; Acute myocardial infarction; Complications

## Introduction

In every year since 1900 except 1918, cardiovascular disease has accounted for more deaths than any other major cause of death in the US [1,2]; in 2010, it directly caused one in three deaths and was an underlying cause of death in ≈1 of every 6 cases [3]. The estimated prevalence of coronary heart disease (CHD), acute myocardial infarction (AMI), and chest pain in USA is 15.7, 7.6 and 7.8 million, respectively [3]. CHD is estimated to escort approximately 1.76 million admissions per year in the USA [4]. Projections show that by 2030, prevalence of CHD will increase ≈18% from 2013 estimates [3].

Approximately 1.1 million Americans will have a new or recurrent AMI each year [3]. Among those, 950,000 will have chest pain, 150,000 will be silent, and 15% will die due to this AMI. In the last decade there was a decline in the occurrence of ST segment elevation myocardial infarction (STEMI) [5], however the mortality rate increases for every 30 minutes that elapses before a patient with ST-segment elevation is recognized and treated, mostly due to secondary complications [6].

STEMI is a clinical syndrome defined by characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic ST elevation and subsequent release of biomarkers of myocardial necrosis [7]. Chest pain usually occurs due to the ischemia resulting from AMI. Chest pain is the widespread symptom at presentation in patients with AMI [8,9]. A recent study found that 93.1% out of 331 AMI patients complained of chest pain [10], which was severe for approximately 85% of the sample. Another recent study found that 98.7% of non-diabetic and all diabetic patients have chest pain [11].

Nevertheless, some patients are hospitalized for AMI without this symptom. A recent study [12] showed that 65% out of 893 patients did not have it. Elderly and diabetic patients are more likely to be the ones who have this situation [8]. However, an asymptomatic (silent) AMI, with no pain, is not necessarily less severe than a symptomatic event; indeed, these subgroups sometimes have the worst outcomes [13-16], particularly as they tend to delay seeking medical attention [17,18]. In a previous study about chest pain in acute myocardial infarction among diabetic and non-diabetic patients, all diabetic patients with AMI complained of chest pain [11].

The relationship between pain and complications can be simplified as follows. The sympathetic nervous system (SNS) is stimulated by pain [19], which triggers a cascade of physiological responses that increase myocardial oxygen consumption [20], enhance cardiac vascular reactivity [21], promote platelet aggregation [22] and lower the dysrhythmic threshold [19]. Chest pain severity depends on the presence

and rigorousness of myocardial ischemia [23,24]. This in turn depends on multiple factors influencing the relationship between oxygen supply and demand in the myocardium at risk. Factors that increase heart work load will increase oxygen demand, in turn increasing pain [8].

Pain in ICU is associated with higher rates of complication [25,26], morbidity and mortality if untreated properly. In a study checking the effect of reperfusion on in-hospital mortality after AMI [27], pain was the most important factor in mortality. A study of the presence or absence of chest pain in 422 patients with suspected AMI [28] found that patients whose chest pain persisted or returned during the initial Emergency Department (ED) evaluation had a 2.3 times greater risk of interventions, a 1.7 times greater risk of complications, a 3.8 times greater risk of death producing complications, and a 2.4 times greater risk of developing AMI. Assaad et al. [23] conducted a study to check the effect of duration of chest pain on development of AMI and mortality after 30 days. They found that patients with AMI have longer duration of chest pain than those without AMI. Patients with longer chest pain duration were more likely to have AMI and have a poor prognosis at 30 days.

On the other hand, sometimes pain is not related to outcomes. Cox et al. [29] conducted a study to check the effect of presence or absence of chest pain at the time of thrombolysis on in-hospital complications including death, re-infarction, recurrent ischemic events and stroke. They found that there were no significant differences between the two groups in regard to development of these complications.

Interestingly, a comparison of cardiac and long-term mortalities between patients with and without chest pain [30] found that patients without chest pain have higher cardiac and long-term mortality than patients with chest pain. Moreover, they found that the complications (i.e. re-infarction and heart failure) were higher in patients without chest pain. However, unstable angina was more common in the chest pain group. Similarly, Fesmire and Wears [28] found that patients who never experienced chest pain had a three times higher risk of death compared with patients whose chest pain persisted or returned in the ED, and a 2.1 times greater risk of intervention, a 5.2 times greater risk of life-threatening complication, and a 7.9 times greater risk of death compared with patients whose chest pain resolved before arrival in the ED.

Current American College of Cardiology/American Heart Association guidelines for the management of patients with STEMI [7] state that in the absence of a history of hypersensitivity, IV morphine sulfate is the preferred drug for pain relief. Non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors are contraindicated in patients with STEMI because it has been shown in randomized control trials and epidemiological studies that they may be associated with an increased risk of death and complications [31-34]. The same guidelines recommend the use of intravenous beta-blockers and nitrates in patients with persistent ischemic chest pain, if not contraindicated.

European Society of Cardiology (ESC) guidelines [35] for the management of STEMI patients recommend intravenous morphine for relief of ischemic chest pain. Although, intra venous beta-blockers and nitrates are not routinely recommended, they should be considered in selected STEMI patients without contraindications.

Morphine has been used to treat pain for AMI patients since the 1960s, predating the use of reperfusion strategies [8,36,37]. Limited studies [8] checked the effect of morphine in this domain. Despite that, clinical practice guidelines for the management of patients with STEMI strongly recommend the use of morphine for analgesia [7,35], however this recommendation is driven only by expert opinion [8].

Since the 1990s, the following have been the immediate priorities when caring for patients with AMI: 1) pain control, 2) management of cardiogenic shock, 3) reperfusion of the myocardium, 4) cardiac monitoring for complications, and 5) management of anxiety [38]. With development of different treatment options for AMI, it is highly recommended that the health care team manage the cause of the ischemic pain rather than simply mask it with analgesia. Therefore, the major goal of this study was to check the effect of pain and morphine use on complication rates early after AMI.

# Methodology

## Research hypothesis

1.There will be a correlation between severity of chest pain and number of complications after AMI.

2.Patients with severe pain (pain score ≥ 7) will have more complications than patients with pain that is not severe (pain score less than 7).

3.Pain scores will be independent predictors for in-hospital complications after controlling for socio-demographics and clinical variables.

4.Patients with severe pain will have longer length of stay (LOS) in the hospital and in the ICU than patients with pain that is not sever.

5.Patients who received morphine will have fewer complications and shorter LOC in the ICU and in the hospital than those who did not receive it.

## Research design, sample and setting

A retrospective descriptive design was used in this study. The study was conducted at three private and one teaching hospital in Jordan. The inclusion criteria of the sample were: a diagnosis of AMI evidenced by elevated cardiac enzymes and electrocardiogram changes; being 18 years old and above; and signed an informed consent. This resulted in 371 patients being included in this study.

## Ethical consideration

Ethical approval for this study was granted by the IRB Committee at the Applied Science Private University, Amman, Jordan (IRB Number: faculty 004). This letter was submitted to the medical and nursing directors of the studied hospitals, who accepted the IRB approval from the Applied Science University. Therefore, permissions to conduct the study within these hospitals were issued to the principle investigators by the medical directors.

## Data collection

An experienced cardiovascular nurse research assistant who had received training in chart reviewing did data collection after patients were discharged from the hospital. Because more than one research assistant collected the data from the sites, inter-rater reliability was tested. Before research assistants began reviewing the charts, they abstracted data from ten practice charts. After research assistants completed the first five charts, the data were compared and differences were resolved. The research assistants then reviewed the last five charts to test inter-rater reliability. Agreement among research assistants was 95%. These ten charts were not included in the data analysis.

## Measurement of variables

All information needed for this study was collected from the medical records after patient discharge. Socio-demographic data included age, gender, marital status and smoking status. Clinical data included history of diabetes mellitus, hypertension, previous AMI, coronary artery disease, angina, coronary artery bypass graft or any other surgery, any percutaneous transluminal coronary angioplasty, or other interventional therapy. Medication used included morphine and any analgesics, thrombolytic agents and beta-blockers. LOS in the ICU and in the hospital, and estimation of worst chest pain on a scale of 0 to 10 in ED before admission to the ICU were also collected.

**In-hospital complication:** Complications were defined similar to our previous studies [4,19,39,40] as the occurrence of any of the following during hospitalization: (i) acute recurrent ischemia evidenced by new onset of chest pain, with ECG changes or hemodynamic instability; (ii) re-infarction evidenced by elevated cardiac enzymes and standard ECG changes; (iii) sustained ventricular tachycardia ( > 15 seconds), or any ventricular tachycardia requiring pharmacological and/or electrical intervention; (iv) ventricular fibrillation; (v) supra-ventricular tachyarrhythmia with hemodynamic instability; (vi) acute pulmonary edema; (vii) cardiogenic shock; and (viii) in-hospital death.

**Morphine use:** Medical records were reviewed to determine whether morphine was administered to patients in the ED before they were admitted to the ICU. The total dose the patients received in ED was documented in mg. Most of the complications mentioned above occur in ED [19,39], or in the first 24-72 hours after admission to ICU [19,39]. For this reason, we did not include the use of morphine in the ICU to ensure the occurrence of temporality. The use of morphine medication then was scored either 0 to indicate 'no use', or 1 to indicate 'use'.

**Length of stay:** Medical records were reviewed to determine the LOS in the ICU and in the hospital. The LOS was measured in days.

## Data analysis

SPSS software version 20.0 was used to analyze the data (SPSS Inc., Chicago, IL, USA). Pearson correlation was used to test for correlation between pain and number of complications (hypothesis 1). Hypotheses 2, 4 and 5 were tested using independent sample t-tests. To make sure that the socio-demographic and clinical variables did not affect the effect of morphine use on the complication, we compared the two groups who received morphine and those who did not in regard to these characteristics. Any significant difference was added to a regression model. To check hypothesis number 3, hierarchical logistic regression was used. In the first block, age and gender were entered. In the second block, history of diabetes mellitus, hypertension, myocardial infarction, beta blocker use and smoking history were entered. In the final block, pain scores were entered. Alpha was set at 0.05 for all analyses. The results of the logistic regressions are reported as odds ratios with 95% confidence intervals.

# Results

Socio-demographic and clinical characteristics of the sample are presented in (Table 1). Approximately two-thirds of the sample was males, with a mean age of 67.7 ± 10.8 years. Most of the patients were hypertensive, with a history of previous angina. Complications developed in 22.6% of the sample (Table 2). Re-ischemia was the highest complication developed, while re-infarction was the lowest. Patients with severe pain have more complications than those with mild and moderate pain. This means that there is a dose response relationship between pain level and mean number of complications, which is reflected by the correlation coefficient ($r = .48$, $p < .001$).

**Table 1** Socio-demographic and clinical characteristics.

| Variable | Total sample (n=371) | Received morphine (n=71) | No morphine (n = 300) |
|---|---|---|---|
| Gender | | | |
| Male | 250 (67.9) | 39 (54.9) | 211 (70.3) |
| Female | 121 (32.1) | 32 (45.1) | 89 (29.7) |
| Age | 67.7 ± 10.8 | 68.6 ± 11.5 | 67.5 ± 10.6 |
| Chest pain severity | 3.7 ± 2.6 | 4.3 ± 2.8 | 3.6 ± 2.5 |
| Hypertension | 270 (72.8) | 41(57.8) | 229 (76.3) |
| Diabetes | 143 (38.5) | 17 (23.9) | 126 ( 42.0) |

| | | | |
|---|---|---|---|
| Previous AMI | 231 (62.0) | 57 (80.3) | 174 (58.0) |
| Previous angina | 315 (84.9) | 25 (83.3) | 146 (85.9) |
| Previous CABG | 215 (58.0) | 47 (66.2) | 168 (56.0) |
| Stent use | 190 (51.2) | 46 (64.7) | 144 (48.0) |
| Hospital complication | 84 (22.6) | 27 (38.0) | 57 (19.0) |
| Smoking | | | |
| Never | 120 (32.3) | 21 (29.6) | 99 (33.0) |
| Current | 90 (24.3) | 21 (29.6) | 69 (23.0) |
| Former | 161(43.4) | 29 (40.8) | 132 (44.0) |

Values are given as frequency (%) or mean ± SD.

**Table 2** Specific complications developed and their percentages.

| Complication developed | *Number of patients (%) |
|---|---|
| Acute recurrent ischemia | 75 (20.21) |
| Pulmonary edema | 12 (3.24) |
| Supra-ventricular tachyarrhythmia | 9 (2.43) |
| Sustained ventricular tachycardia | 6 (1.62) |
| Re-infarction | 6 (1.62) |
| Cardiogenic shock | 5 (1.38) |
| In-hospital death. | 4 (1.08) |
| Ventricular fibrillation | 3 (0.81) |

*More than one patient developed more than one complication.

Among all the variables that were used in the logistic regression, only pain scores and history of previous AMI were the independent predictors of in-hospital complications. Patients with severe chest pain were at 4.54 times higher risk for developing complications than other patients. History of previous AMI increased the risk for developing complications by 141% (Table 3). Patients with severe pain had more complications, and stayed in the ICU and in the hospital longer than other patients (Table 4).

**Table 3** Independent predictors of in-hospital complications.

| Predictor | OR | 95% confidence interval | B | Wald | P- value |
|---|---|---|---|---|---|
| Age | 1.01 | 0.96-1.06 | 0.01 | 0.13 | 0.72 |
| Gender | 0.34 | 0.10-1.15 | -1.07 | 2.99 | 0.08 |
| Previous AMI | 2.41 | 1.05-5.45 | 0.88 | 3.01 | 0.04 |
| Diabetes | 1.46 | 0.38-5.61 | 0.38 | 0.38 | 0.58 |
| Hypertension | 0.25 | 0.50-1.24 | -1.40 | 2.90 | 0.90 |
| Use of beta blocker | 0.36 | 0.03-4.68 | -1.02 | 0.61 | 0.44 |
| Smoking | 1.92 | 0.43-8.46 | 0.65 | 0.74 | 0.39 |
| Pain scores | 4.54 | 3.05-6.76 | 1.51 | 55.22 | 0.00 |

**Table 4** The effect of chest pain on in-hospital complications and LOS.

| Item | Pain levels* | Means | SD | P Value |
|---|---|---|---|---|
| Complications | S | 1.65 | 1.04 | < .001 |
| | NS | 0.16 | 1.14 | |
| ICU LOS | S | 5.98 | 6.13 | < .05 |
| | NS | 3.37 | 3.04 | |
| Hospital LOS | S | 7.34 | 14.5 | < .001 |
| | NS | 4.17 | 6.99 | |

*S = severe, NS = not severe (mild and moderate)

Only 71 patients (19.1%) used morphine, with a minimum dose of 2 mg, maximum dose of 10 mg and a mean of 4.6 ± 2.4mg. Those patients were more likely to be female, diabetic and with a history of previous AMI. Patients who received morphine reported more pain (mean [SD], 4.3 [2.8] vs. 3.6 [2.5], P < .05) than those who did not. However, the use of morphine did not have any protective effect against the development of complication, nor on the LOS in the ICU or in the hospital.

## Discussion

This study was designed specifically to examine the effects of pain and administration of morphine on in-hospital complication rates after AMI. It was hypothesized that pain would increase these complications, and early administration of morphine would eradicate this relationship. This proposition was based on the principle that pain stimulates the SNS [19], resulting in a series of physiological responses including enhanced coronary vascular tone [21], platelet aggregation [22], increased myocardial oxygen consumption and lowered

threshold for dysrythmias [41]. Combined, these responses would increase patients' susceptibility to ischemic and dysrhythmic complications, which usually occur in the first 48 to 72 hours after AMI. During this period, the administration of morphine should be effective in controlling this mechanism.

The results of this study suggested that pain increased the rate of complications early after AMI, and pain scores were independent predictors of these complications. This conclusion is supported by other studies [23,27,28] checking the effect of pain on complications and mortality after AMI. Chest pain was the most important factor affecting the mortality [27]. Patients with chest pain were at higher risk of developing complications and AMI [23,28]. Further support of these results comes from the observations that anxiety, which works with the same mechanism as pain (e.g. stimulation of the SNS), has the same outcomes. Previous studies checking the effect of anxiety on complications early after AMI showed that anxiety increased the complications [19,39-40]. Also, anxiety scores were independent predictors of complications after AMI. In addition, severe pain was associated with increased LOS in the hospital and in the ICU. Again, this result is consistent with studies checking the effect of anxiety of the LOS in the hospital and in the ICU showing that anxiety has negative outcomes on the LOS [19,39-40].

The results of our study suggested that administration of morphine did not eliminate the effect of pain on in-hospital complications or on LOS. In the meantime, there have been no prospective studies evaluating the use of morphine for this indication. The AHA and European guidelines recommended that patients should receive the minimum dose required (4-8 mg) to achieve chest pain relief. Furthermore, the guidelines stated that NSAIDs and COX-2 inhibitors are contraindicated.

In this study the mean dose of morphine for those who received it (n = 71, 19.1%) was 4.6 ± 2.4 mg, and none of the sample received NSAIDs or COX-2 inhibitors. This means that the health care providers were in compliance with the guidelines; however the patients did not experience a positive effect of morphine on the outcome of interest.

In order to understand the reason behind these results, firstly we should understand how morphine works and its major side effects. Narcotic analgesics, including morphine, mimic the actions of brain peptides by binding to cellular receptors which activate the endogenous pain-modulating systems [8]. The majority of morphine effects are due to interaction with μ receptors, found mainly in the brain and gastro-intestinal tract [8]. The activation of brain receptors results in analgesia, sedation, respiratory depression and euphoria. Hypoventilation is another effect for this stimulation, which may cause hypoxemia, an unwanted event in AMI.

Activation of receptors in the gastro-intestinal tract delays the transit time from the stomach to the intestine and reduces intestinal and pancreatic secretions [8]. Nausea and vomiting, common side effects of morphine administration, are thought to occur due to the interaction with μ receptors in the chemoreceptor trigger zone and the vomiting center in the medulla [42]. Moreover, high doses may cause hypotension due to vasodilatation [8,37].

Keeping the side effects of morphine in mind, some previous studies showed that its use resulted in increased in-hospital mortality, such as Meine et al. [43]. However, this study was not a randomized controlled one; furthermore, morphine was given to higher-risk patients. Another study [44] showed that STEMI patients who did not use morphine had a significant improvement in the ECG-based primary endpoint (potentially reflecting better myocardial reperfusion).

Explanations proposed for the results of our study and other studies showing negative effects of morphine include drug-drug interaction. Patients with AMI usually receive a mixture of drugs, which increases the value of this theory. Antiplatelets are one of the routinely given medications for AMI. Some previous studies [44-46] showed that interaction between morphine and anti-platelets resulted in delayed onset time for the latter, attributed to the inhibition of gastric emptying by morphine, thereby delaying absorption and possibly resulting in decreased peak plasma levels of orally administered drugs [47,48]. Another explanation that might be applicable in the context of our study is that the percentage of those who received morphine (19.1%) compared to those who did not is low. Randomized controlled trials with larger sample sizes are recommended to check this effect.

New studies [8] recommend the use of other alternative strategies to reduce pain. Drugs that might be able to influence chest pain in AMI patients are presented in Table 5. Previous studies [49] showed that intravenous paracetamol (1 g) or aspirin (300 mg) were able to reduce mild and moderate chest pain. Additionally, early administration of aspirin with heparin increased artery patency and reduced chest pain [50]. Furthermore, it has long been documented that beta-blockers [51] and nitrates [52] are able to reduce AMI-related chest pain. Lastly, reperfusion should be considered the perfect chest pain control strategy [53].

**Table 5** Drugs influencing chest pain in AMI patients.

| Drug class | Drug type | Comments |
|---|---|---|
| Nonopioid analgesics | Paracetamol | Unproven efficacy |
| | Ibuprofen | Contraindicated in AMI |
| Antiplatelets | Aspirin | Allergic reactions |
| | | Bleeding |
| Anticoagulants | Heparin | Thrombocytopenia |
| | | Bleeding |
| Thrombolytics | Streptokinase | Bleeding |
| Anti-ischaemic | Beta-blockers | Increase heart failure and atrioventricular blocks |
| | Nitrates | Hypotension |

Keeping this in mind, selective use of intravenous morphine could be an appropriate therapy for AMI patients who have chest pain persisting despite initial therapy based on aspirin

(with or without heparin) and anti-ischemic drugs [54]. It has been shown previously that standard dose of morphine (4-8 mg) works better to decrease chest pain than increased Metoprolol dose after initial use.

## Conclusion and Recommendations

This study showed that pain was associated with increased risk of complications and LOS in the hospital generally, and in the ICU in particular, increasing mortality and morbidity among patients and the burden on health systems. AMI protocols should be incorporated when managing such patients. Appropriate interventions should be implemented to those patients as early as possible to prevent these complications. It has been shown in previous studies that morphine has serious side effects in patients with AMI. In this study, its use did not result in reduction of the complication rates nor in LOS, thus it is recommended that other types of pain relief methods (e.g. treating the cause of pain; addressing the imbalance between oxygen supply and demand) should be incorporated in the protocols. Recent studies [8] recommended the use of intravenous anti-platelets (i.e. aspirin) ± heparin, IV BB and/or nitrates (if not contra-indicated) before resorting to the use of morphine, to decrease oxygen consumption and enhance blood supply to myocardium. After that, the patients will be assessed for pain and the following protocol is recommended.

If the patient has a persistent severe chest pain (score ≥ 7) even with the use of above mentioned medications, then morphine 4-8 mg should be given. If the pain is not severe, then paracetamol 1 gm should be given. Finally, myocardial reperfusion should be done.

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