The Prevalence and Outcomes of Morphine Use in the Initial Management of Patients with Acute Myocardial Infarction

by

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Background: Morphine has been historically used for the initial management of pain in patients with suspected acute myocardial infarction (MI). There is controversial evidence that suggests that morphine use is associated with adverse outcomes in both ST-elevation and non-ST-elevation MI. Purpose: We sought to define the prevalence and outcomes of morphine use in the initial management of patients with suspected acute MI in the emergency department. Theoretical Framework: Some studies suggest that morphine delays and attenuates the action of anticoagulants in patients with MI, which might lead to adverse cardiac outcomes. Methods: This was a secondary analysis of Electrocardiographic Methods for the Prompt Identification of Coronary Events (EMPIRE) study. EMPIRE was a prospective, observational, cohort study that enrolled consecutive chest pain patients transported by ambulance to three UPMC-affiliated tertiary care hospitals. Pertinent clinical data were obtained from charts, including intravenous morphine administration up to procedural intervention (independent variable). The presence of the following clinical outcomes (dependent variables) was adjudicated by two independent reviewers: infarct size (defined by peak troponin level), myocardial dysfunction (defined by left ventricular ejection fraction), and major adverse cardiac events (MACE, defined as death, fatal ventricular arrhythmia, acute heart failure, pulmonary edema, cardiogenic shock, reinfarction, or repeat catheterization within 30 days of indexed admission). Results: Our sample included 155 patients with confirmed

acute MI (age 64±16, 42% females, 29% Blacks). Patients who received morphine (n=58, 37%) were older and had higher pain scores, but there were no other baseline differences clinical characteristics. In multivariate analyses, morphine use was not associated with infarct size, myocardial dysfunction, or MACE after controlling for MI type and other potential confounders. Conclusions: In this cohort, we found that morphine use in the initial management of acute MI is not associated with increased risk of adverse cardiac outcomes.

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1.0 INTRODUCTION

According to the Centers for Disease Control and Prevention, in 2010, upwards of 7 million people visited an emergency department (ED) with chest pain nationwide; additionally, ischemic heart disease accounted for about 2.3% of ED discharge diagnoses (2014). Identifying patients with acute cardiovascular distress is a top priority, in order to maintain viable tissue perfusion and minimize damage. Such life-threatening etiologies include acute myocardial infarction (AMI), aortic dissection, cardiac tamponade, tension pneumothorax, and pulmonary embolism. Beyond the immediate life-threatening causes, chest pain can be precipitated by a wide range of etiologies, including pericarditis, esophagitis, cardiomyopathy, heart failure, pulmonary disease, valvular disease, musculoskeletal pain, etc. (Weinstock et al., 2015). Accordingly, identifying the exact etiology of chest pain requires extensive diagnostic testing and constitutes an ongoing challenge in emergency practice. Too often, patients are discharged with unspecified chest pain, only equipped with the instructions explaining the signs and symptoms that warrant a return to the ED. In a meta-analysis containing studies published between 1996 and 2010, the prevalence of patients diagnosed with nonspecific chest pain was 44% (Ruddox, Mathisen, & Otterstad, 2012).

Inappropriate specificity of diagnostics, poor clinical judgement, and noncompliance with hospital procedures results in patients being discharged prematurely or unnecessarily admitted. In a study of patients admitted with suspected AMI, there was a 9% rate of non-AMI diagnosis at discharge (Barrabés et al., 2018). An overabundance of chest pain patients admitted to a hospital

for observation or diagnostics presents a burden on healthcare systems, consumption of resources, and unnecessary stress for the patient (Weinstock et al., 2015).

Due to the vague nature of diagnosing chest pain, the treatment of nonspecific chest pain presentation becomes managing the symptoms rather than diagnosing the underlying cause. Therefore, to accurately and effectively manage and diagnose chest pain, guidelines have adapted based on the best evidence-based clinical practice. Guidelines are established in hospital protocols to assist the healthcare providers through the assessment, diagnosis, planning, intervention and evaluation phases of acute treatment. Protocols are imperative to efficiently and effectively stabilize acutely sick patients. In the emergency setting, it is a race against time. Furthermore, when a patient is experiencing an ischemic emergency, "time is tissue," which is why time must be prioritized towards effective and beneficial interventions. Across the cardiac literature, there is a big focus on reducing total ischemic time (Peterson, Syndergaard, Bowler & Doxey, 2012).

When a patient presents with chest pain to an emergency setting such as the ED, protocols are followed to assess and diagnose the underlying cause. A history and physical, a 12-lead electrocardiogram (ECG), and a chest X-ray are usually the first actions taken because they are the quickest and least invasive diagnostic procedures that can rule out ACS or other life-threatening conditions (Hollander & Chase, 2016). Further diagnostic testing may include Computed Tomography (CT) coronary angiography, Nuclear Stress testing, echocardiography, and diagnostic catheterization to determine the extent of coronary artery disease and ischemic myocardium (Sørgaard et al., 2017). Many of these diagnostic tests are performed during the inpatient stay, which may unnecessarily contribute to the burden on healthcare resources.

An AMI is defined as acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cardiac troponin values (Thygesen et al., 2018).

Evidence of myocardial ischemia may be detected with an ECG. Furthermore, the presence of ischemic symptoms may present as diffuse or localized pain in the chest, mandible, epigastric or upper extremity regions. Ischemic symptoms may alternatively present as dyspnea, nausea, indigestion, shortness of breath, or diaphoresis (Amsterdam, et al., 2104).

ECG changes such as ST-segment elevation, ST-segment depression, and T-wave inversion may be indicative of cardiac ischemia. An ST-elevation myocardial infarction (STEMI) is a thrombotic coronary event that results in a transmural occlusion of the coronary artery leading to myocardial ischemia and infarction (Montecucco, Carbone & Schindler, 2015). However, if the ECG is unremarkable, further testing such as serial troponin assays can be drawn to rule out a non-STEMI (NSTEMI). In the absence of ST-elevation, NSTEMI can be diagnosed if there is significantly high troponin serum value, which is a unique enzyme that has a delayed release from infarcted myocardium. If AMI is suspected, then the patient may require emergent coronary catheterization with percutaneous coronary intervention (PCI) or fibrinolytic therapy to re-cannulate the coronary artery and reperfuse the myocardium. Unfortunately, the majority of patients may spend several hours on a cardiac observation unit for evaluation of potential elevation in serum troponin, furthermore, contributing to significant consumption of hospital resources and unnecessary costs (Rivero, 2017).

A history and physical, an ECG, and a serial troponin is the generic diagnostic workup for any patient with suspected AMI. Consequently, these diagnostic tests may take up valuable time which can be costly to myocardial salvage. In the circumstances of AMI, the main goal of treatment is to reperfuse the myocardium as soon as possible to minimize infarcted tissue and reduce major adverse cardiac outcomes (Montecucco et al., 2015). In order to compensate for the delayed action of ultimately recannulating the occluded coronary artery, institutional protocols, algorithms, and

decision-making models have been fabricated to direct healthcare providers in the acute treatment of STEMIs and NSTEMIs (Shah & Nathan, 2018). Morphine, oxygen, nitroglycerin, and aspirin (MONA) has been the gold standard treatment in minimizing myocardial damage and infarction for patients experiencing AMI in the emergency setting (Amsterdam et al., 2014; Kleinman et al., 2018; Kristensen & Aboyans, 2018; O'Gara et al., 2013; Roffi et al., 2016).

Priority interventions for AMI include pain management which may include morphine administration depending on the severity and persistence of chest pain. Given the pathophysiology of an AMI, pain management is a priority intervention. Chest pain develops from myocardial ischemia and hypoxemia because there is an imbalance between oxygen supply and oxygen demand in the myocardium (Thygesen et al., 2018). Pain increases sympathetic activation which leads to increased heart rate and blood pressure, thus increasing cardiac workload resulting in a greater oxygen demand and further damaging myocardium. In some studies, the duration and severity of chest pain has been associated with more complications (AbuRuz, 2016; Assaad et al., 2013; Herlitz et al., 1984; Herlitz, Richter, Hjalmarson & Holmberg, 1986). In order to break that positive feedback loop, pain management is a top priority to prevent unnecessary additional damage to myocardium, especially important in the early stages of AMI.

When AMI is indicated at any point, it is necessary to administer MONA in accordance with AMI guidelines. However, even with the help of guidelines, controversy over the best treatment is made evident by conflicting opinions introduced by emerging clinical research. Recently, evidence-based medicine suggests the use of morphine in AMI patients may not be the best treatment (Meine et al., 2005).

2.0 BACKGROUND

Guidelines recommend morphine administration in AMI patients because morphine's analgesic effects control pain, reduce anxiety, and decreases heart rate, blood pressure, and venous return (Everts, Karlson, Herlitz & Hedner, 1998). Another added benefit is that it is conveniently accessible and easily administered intravenously in an emergency setting. However, emerging literature challenges the benefits of morphine use in AMI patients (McCarthy, Bhambhani, Pomerantsev & Wasfy, 2017).

When considering the latest guidelines for AMI, the most recent (2013) American College of Cardiology (ACC) Foundation and American Heart Association (AHA) guidelines state, "In the absence of a history of hypersensitivity, morphine sulfate is the drug of choice for pain relief in patients with ST-segment elevation MI (STEMI)." These guidelines have no formal class of recommendation (COR) or designated level of evidence (LOE) supported. On the other hand, in the updated 2017 European Society of Cardiology (ESC) STEMI guidelines gives opioids a class IIa COR and a LOE 'C' based on expert opinion. This is a drawback from a class I COR in the 2012 ESC STEMI guidelines. The 2017 ESC STEMI guidelines comes with a disclaimer that, "morphine use is associated with a slower uptake, delayed onset of action, and diminished effects of oral antiplatelet agents."

The most recent ACC/AHA NSTEMI guidelines (2014) support morphine use with a class IIb recommendation, following a steady downgrade from class I in the 2007 guidelines revision. The most recent ESC NSTEMI guidelines (2015) provide no COR, however, they acknowledge emerging research by disclaiming "morphine may slow intestinal absorption of oral platelet inhibitors." There is a strong need for research regarding morphine and its benefits. A LOE 'C' is

the weakest tier supported by research evidence. Healthcare providers are beginning to acknowledge research-based medicine and reconsider the effectiveness of morphine for analgesic effects in AMI patients. This is made evident by the subtle changes in guidelines made over that past decade. These changes made over the past two decades can be visualized in Table 1.

Table 1: History of Morphine Guidelines

ACC/AHA Guidelines	Class of Recommendation	Level of Evidence
1999 Acute MI	I	-
2004 STEMI	I	C
2007 NSTEMI	IIa	B
2013 STEMI*	**-**	**-**
2014 NSTEMI*	**IIb**	**B**

ESC Guidelines	Class of Recommendation	Level of Evidence
2002 Chest Pain	I	C
2012 STEMI	I	C
2015 NSTEMI*	**-**	**-**
2017 STEMI*	**IIa**	**C**

*** Indicates most recent guidelines**

A pivotal part to myocardial salvage in the immediate treatment of AMI involves oral anticoagulation therapy, such as aspirin and P2Y12 receptor antagonists (Yusuf et al., 2001). It is believed that a suboptimal response to an antiplatelet regimen may be associated with adverse cardiovascular and cerebrovascular outcomes. Also, poor inhibition of platelet aggregation may lead to a higher risk of stent thrombosis in such patients (Buonamici et al., 2007; Cuisset et al., 2006; Gurbel, Bliden, Hiatt & O'Connor, 2003; Matetzky et al., 2004). For these reasons, early and aggressive anticoagulation therapy is recommended and has shown to improve outcomes in

AMI (Alexander et al., 2008; Cohen & Downey, 2014; Parodi et al., 2013; Patti et al., 2011; Roubille et al., 2012).

Morphine raises concerns that would not support the use in AMI patients. Several common opioid side effects may contradict the desired therapeutic effect. Nausea, vomiting, and inhibition of peristalsis may negatively impact the absorption of oral medications. Anticoagulants prevent additional myocardial damage by inhibiting platelet accumulation in the potentially thrombus-occluded coronary artery. In basic experimental studies, evidence suggests morphine decreases the absorption and delays the onset of platelet inhibition in the co-administration of morphine and oral anticoagulants, specifically P2Y12 receptor antagonists such as clopidogrel, ticagrelor, and prasugrel (Hobl et al., 2014; Hobl et al., 2016a; Hobl et al., 2016b; Parodi et al., 2015; Silvain et al., 2016; Thomas et al., 2016). For this reason, there is a need for research that explores the outcomes of AMI patients who receive morphine.

Morphine administration is significantly associated with increased pain severity (AbuRuz, 2016; Deng et al., 2018; Herlitz et al., 1986), however, recent studies suggest pain severity has not been found to increase the probability of AMI or major adverse cardiac events (MACE) (Body et al., 2016; Edwards et al., 2011; Galinski et al., 2015). Therefore, morphine administration may be unnecessarily putting AMI patients at an increased risk of adverse outcomes due to a prothrombotic state.

Discussed further is how recent literature has been inconclusive regarding the benefits and risks related to morphine administration in AMI patients. Research is focused on studying the clinical implications of morphine administration such as length of hospital stay, myocardial infarction size, and in-hospital and 30 days MACE. For example, several articles reported morphine administration is associated with a larger infarct size in STEMI patients who undergo a

primary PCI (Bellandi et al., 2016; de Waha et al., 2015; Farag et al., 2018). Furthermore, in two large retrospective studies observing NSTEMI cases, morphine was associated with larger infarct size, longer length of stay (McCarthy et al., 2017), and increased hospital mortality (Meine et al., 2005). On the other hand, four large scale studies published in the last three years have concluded that there is no excess risk with morphine administration to STEMI patients in terms of infarct size and 1-year MACE (Bonin et al., 2018; Gwag et al., 2017a; Gwag et al., 2017b; Puymirat et al., 2015). There is controversy regarding the efficacy and safety of morphine administration in AMI patients.

3.0 PURPOSE AND SPECIFIC AIMS

The purpose of this study is to evaluate the adverse effects of morphine use in AMI patients using a cohort of 2,065 patients who presented to a UPMC ED via EMS with a chief complaint of chest pain. Findings can inform the appropriateness of morphine for use in patients with AMI.

Specific Aim 1: Determine the prevalence of morphine use among patients treated for chest pain pre-hospital and in-hospital:

Aim 1(a). What is the prevalence of morphine administration among AMI patients? STEMI? NSTEMI?

Aim 1(b). Are there demographical and clinical differences between patients who did and did not receive morphine?

Specific Aim 2: Evaluate the relationship between morphine administration and clinical outcomes in patients with STEMI vs. NSTEMI:

Aim 2(a). Is there a relationship between morphine use and size of infarct in STEMI vs. NSTEMI patients after controlling for potential confounders?

Aim 2(b). Is there a relationship between morphine use and myocardial dysfunction in STEMI vs. NSTEMI patients after controlling for potential confounders?

Aim 2(c). Is there a relationship between morphine use and 30-day MACE in STEMI vs. NSTEMI patients after controlling for potential confounders?

4.0 METHODS

4.1 DESIGN AND SETTING

This was a secondary analysis of Electrocardiographic Methods for the Prompt Identification of Coronary Events (EMPIRE) study (Al-Zaiti, Martin-Gill, Sejdić, Alrawashdeh, & Callaway, 2015). EMPIRE is a prospective, observational, cohort study that enrolled consecutive chest pain patients transported by ambulance to three University of Pittsburgh Medical Center (UPMC)-affiliated tertiary care hospitals, UPMC Mercy, UPMC Shadyside, and UPMC Presbyterian. EMPIRE is an ongoing study that recruits patients into three phases: cohort 1 (2013–2014, n=2,065), cohort 2 (2014–2016, n=3,350), and cohort 3 (2016–2017, n=1,785). This secondary analysis includes patients in cohort 1 because the clinical outcomes adjudication for cohorts 2 and 3 is still ongoing.

The EMPIRE study was approved by the Institutional Review Board (IRB) of University of Pittsburgh. This study is minimal risk as it collected routine care data and there is no patient contact; data were extracted from electronic medical records by reviewers blinded to study outcomes. All extracted data were de-identified before storage and a linkage list was kept separate from the data; both measures were taken to reduce the risk of breach of confidentiality. The current secondary analysis was approved by Dr. Salah Al-Zaiti.

4.2 STUDY POPULATION AND SIZE

The cohort included 2,065 chest pain patients transported to the ED by ambulance. A total of 155 patients with confirmed AMI were included in the study. The presence of AMI was adjudicated by two independent reviewers after review of course of hospitalization. MI type (STEMI vs. NSTEMI) was retrieved from cardiac catheterization report as determined by the interventional cardiologist at time of patient care. Figure 1 demonstrates the patient flow diagram.

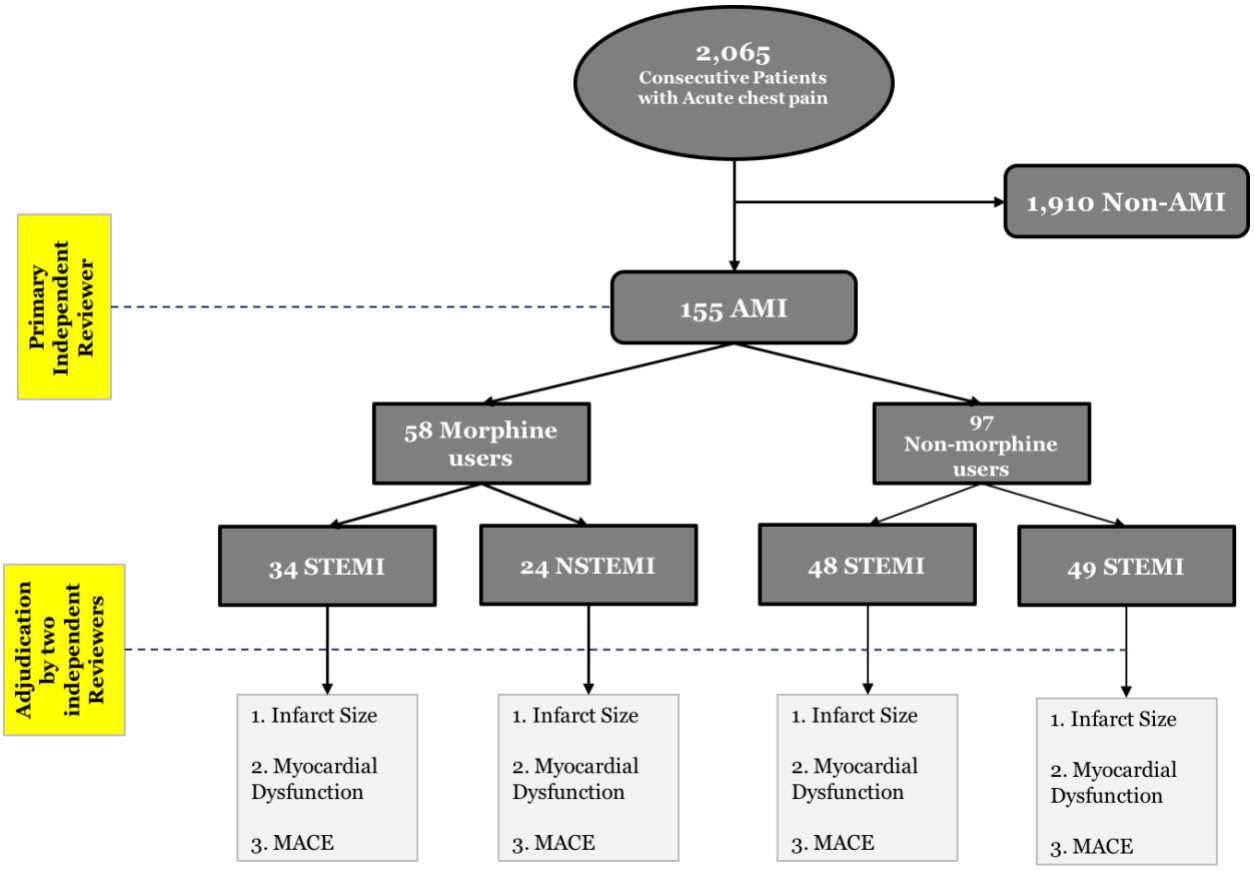

Figure 1: Distribution of Sample

4.3 VARIABLES AND DATA COLLECTION

The morphine group included patients who received intravenous (IV) morphine during prehospital transport or during in-hospital stay prior to catheterization. This includes administration up to the point of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Patients with a medically managed MI who received IV morphine were included in the morphine group. If morphine was administered post-procedural, the patient was included in "no morphine administration" group.

Each patient chart was systematically reviewed by a single primary reviewer. Age, sex, race, body mass index (BMI), and smoking history demographics were retrieved in all the charts. The independent variable included pre-procedural IV morphine administration. Dependent variables included past medical history (PMH), culprit lesions defined by a coronary vessel 70% occluded, and presenting signs and symptoms. Presenting signs and symptoms retrieved included prehospital heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, pain severity prior to morphine administration, shortness of breath, gastrointestinal (GI) upset, and diaphoresis. Initial blood creatinine value and blood glucose value were retrieved with the first blood labs prior to intervention. Additional data included admission time/date, length of stay, morphine dose and time of first morphine administration, time of first three consecutive troponin blood values, and pre-procedural aspirin and nitroglycerin administration, and oxygen administration at the ED.

Two independent reviewers adjudicated the following primary clinical outcomes: infarct size, myocardial dysfunction, and 30-day major adverse cardiac events (MACE). Infarct size was defined by the peak serum troponin level during entire length of hospitalization. A higher spike in serum troponin is associated with increased myocardial infarction (Mohammad et al., 2018).

Myocardial dysfunction was defined by left ventricular ejection fraction (LVEF). LVEF was obtained from the post-procedural echocardiogram. A reduced LVEF post-MI is indicative of decreased myocardial function and efficiency due to presumed ischemic damaged or infarct myocardium. This is associated with increased incidence of heart failure with worse long-term outcomes (Ndrepepa., 2018). The 30-day MACE was defined as all cause death, fatal ventricular arrhythmia, acute heart failure, pulmonary edema, cardiogenic shock, re-infarction, or repeat catheterization within 30 days of indexed admission. Primary clinical outcomes and elements of MACE were defined in congruence with ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials (2015). Patient charts were followed for 30 days after discharge and clinical data was included in the cases of repeat ED or in-hospital admission.

4.4 STATISTICAL ANALYSIS

Level of significance was set at $p<0.05$ for two-sided hypothesis testing. SPSS Statistics software version 24 of International Business Machines (IBM) Corporation in Armonk, New York, was utilized to process the data. Continuous variables were reported as means ± SD or median [25^{th} – 75^{th} percentiles], categorical variables were reported as n (%). Groups (morphine administration vs. no morphine administration) were compared using t-test for continuous variables and chi-square for categorical variables. Univariate and multivariate models were constructed for each outcome variable. Simple linear regression was used for peak troponin level (surrogate for infarct size) and LVEF (surrogate for myocardial dysfunction). Logistic regression was used for 30-day MACE. Variables significant at $p<0.10$ in univariate analysis were entered in backward selection method in multivariate analysis. All models were computed separately for

patients with STEMI vs. NSTEMI. Log transformation was used for variables that were not normally distributed, namely peak troponin level that was severely positively skewed.

5.0 RESULTS

5.1 SPECIFIC AIM 1

Specific Aim 1 sought to define the prevalence of morphine administration among AMI patients and evaluate differences in baseline characteristics between those who did and did not receive morphine. Of 2,065 chest pain patients, our study sample included 155 patients with confirmed acute MI (age 64±16, 42% females, 29% Blacks). Among those with acute MI, a total of 97 patients (63%) did not receive IV morphine and 58 patients (37%) received IV morphine. The distribution of AMI patients was observed as 73(47%) NSTEMI and 82(53%) STEMI. Of these, 34/82 (41%) STEMI patients were administered IV morphine, compared to 24/73 (33%) NSTEMI patients who received IV morphine.

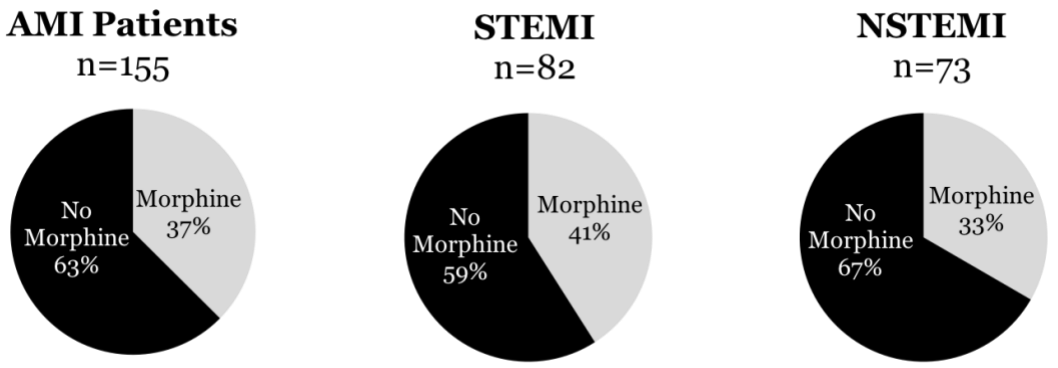

Figure 2: Distribution of morphine administration

Table 1 compares the baseline variables between these two groups. When comparing demographics between the two groups, there were no difference seen in sex, BMI, race, or smoking. There were no variables in PMH or vessel occlusions that were statistically different among the two groups. Patients who received morphine were younger (61±18, p=0.03), presented

with a lower serum glucose (147±51, p=0.019) and reported a higher pain score (7.4±2.6, p=<0.001); no other differences in baseline clinical characteristics were observed. The distribution of treatment was seen as 4/58 (7%) were treated with CABG, 13/58 (22%) were treated with medical management, and 41/58 (71%) were treated with PCI.

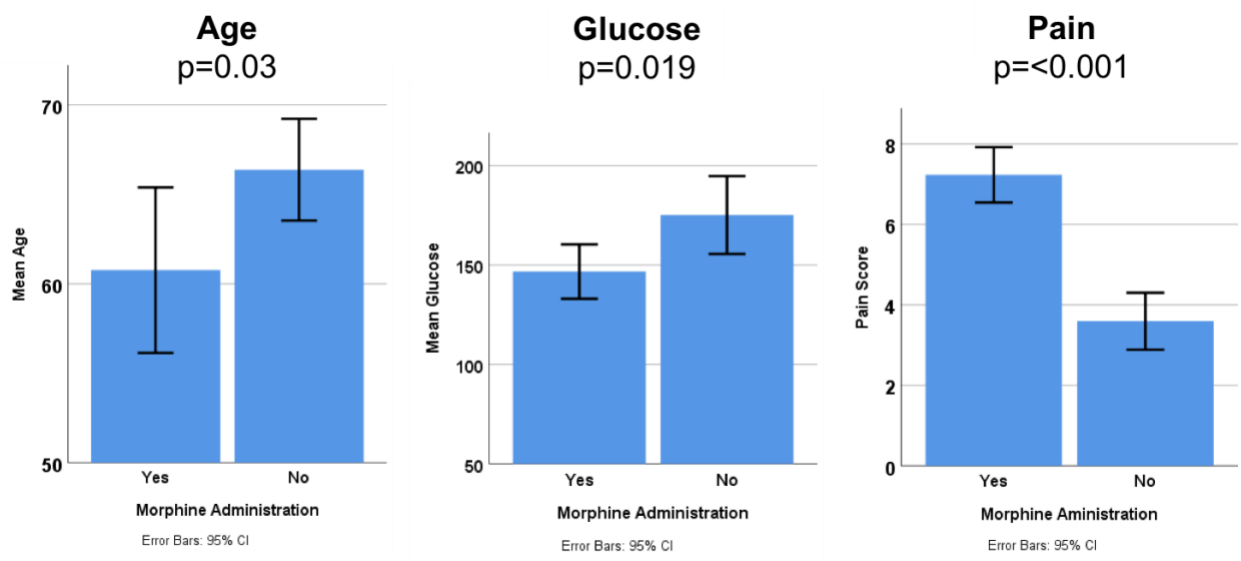

Figure 3: Significant differences among morphine and no morphine administration groups

5.2 SPECIFIC AIM 2

Specific Aim 2 evaluated the relationship between morphine administration and clinical outcomes in STEMI and NSTEMI patients by running two separate models for univariate and multivariate analyses. In the STEMI regression model, there were no univariate or multivariate statistically significant predictors of infarct size. Hypertension (HTN) (p=0.037), respiratory rate (RR) (p=0.048), and oxygen administered at the ED (p=0.002) were independent predictors of infarct size in NSTEMI patients. However, morphine did not predict infarct size in either STEMI or NSTEMI patients (Table 2).

The second regression model observed variables that predicted myocardial dysfunction in the STEMI and NSTEMI groups. Sex (p=0.044), known heart failure (p=0.014), and left anterior descending (LAD) occlusion (p=0.002) were independent predictors of myocardial dysfunction in STEMI patients. Shortness of breath (p=0.049) was the only independent predictor of myocardial dysfunction in NSTEMI patients. Morphine was not statistically significant to predict myocardial dysfunction in either STEMI or NSTEMI patients (Table 3), however morphine was significant in the univariate model for the NSTEMI group.

A third regression model evaluated predictors of 30-day MACE. Systolic blood pressure (p=0.041) and creatinine (p=0.017) predicted 30-day MACE in STEMI patients. Prior CABG (p=0.040) and glucose (0.029) predicted 30-day MACE in NSTEMI patients. There were no other PMH or presenting signs or symptoms that predicted 30-day MACE in either group. Morphine did not predict 30-day MACE in either MI group (Table 4).

6.0 DISCUSSION

The purpose of this study was to evaluate the association of morphine with clinical outcomes in the setting of AMI. Our results have shown that approximately 58(37%) of AMI patients receive IV morphine (34[41%] of STEMI and 24[33%] of NSTEMI). After controlling for MI type and other potential confounders in a multivariate regression model, morphine administration was not associated with infarct size, myocardial dysfunction, or 30-day MACE. Study findings suggest that morphine administration does not lead to excess risk in patients with acute MI.

6.1 PREVALENCE OF MORPHINE ADMINISTRATION

In this study, younger patients and those with higher reported pain score were more likely to be administered IV morphine. Pain has proven to be a major indicator of morphine administration (AbuRuz, 2016; Deng et al., 2018; Herlitz et al., 1986), as well as a younger age (Bonin et al., 2018; de Waha et al., 2015; Gwag et al., 2017b; McCarthy et al., 2017; Puymirat et al., 2015) in several studies involving nonrandomized morphine administration. Morphine is indicated for severe chest pain unrelieved by nitroglycerin. Therefore, this is an expected outcome in our data. We found younger patients report more severe pain when experiencing acute chest pain, therefore are administered morphine more frequently. This can be due to the fact that severe illness is more common in older adults, therefore more attention may be given to diagnostic work instead of pain relief (Platts-Mills et al., 2012).

In addition, we found that those with lower serum glucose level were more likely to be administered morphine. It remains unknown if this is due to altered pain level perception due to poor blood glucose or diabetic control, given that those who presented with a significantly higher blood glucose were not significantly associated with morphine administration.

6.2 SAFETY OF MORPHINE ADMINISTRATION

There is strong evidence that dual antiplatelet therapy (DAPT) has proven to be a pivotal intervention in AMI outcomes. This includes an early loading dose of a P2Y12 inhibitor prior to PCI (Dörler et al., 2011). However, morphine combined with oral P2Y12 inhibitors poses an adverse effect that delays the anticoagulation action in AMI patients (Silvain et al., 2016). For this reason, co-administration of morphine and oral P2Y12 inhibitors raises concerns regarding the safety of morphine use in AMI patients. A recent study utilized myocardial salvage index (MSI) to determine whether IV morphine affects myocardial injury in STEMI patients who received DAPT prior to PCI. They determined IV morphine was not associated with adverse outcomes in myocardial salvage (Gwag et al., 2017b). Our results are consistent with these findings and support that morphine administration is unlikely to lead to profound adverse events in AMI.

6.3 CLINICAL IMPLICATIONS

Several recent studies determining the adverse effects of morphine in STEMI patients do not draw definitive conclusions regarding clinical outcomes. Instead, they provide evidence

concerning surrogate values that serve as prognostic markers of reperfusion success in STEMI patients. Some surrogate values used by these studies to define AMI prognosis are peak troponin, MSI, TIMI-flow, LVEF, and platelet reactivity index (de Waha et al., 2015; Gwag et al., 2017b). Without a longer follow-up duration, conclusions cannot be drawn about the clinical outcomes of IV morphine use in STEMI patients, while only using surrogate values. Evidence from this study shows that IV morphine use in STEMI patients is not associated with 30-day MACE after controlling for confounding variables in a multivariate regression model. This is consistent with the outcomes of one large, nonrandomized, retrospective study of 2,438 STEMI patients who received IV morphine prior to PCI concluding 1-year MACE was not associated with IV morphine (Puymirat et al., 2015). Given the latest published evidence there is no indication that morphine should be contraindicated in STEMI patients. This is based on clinical outcomes of studies that report no association of morphine and MACE, mortality, or length of hospital stay (LOS) (Bellandi et al., 2016; Bonin et al., 2017; de Waha et al., 2015; Farag et al., 2018; Puymirat et al., 2016) .

Contrary to our findings, Meine, T.J. et al. (2004) evaluated the association of IV morphine use and ACS outcomes in a sample of 17,003 NSTEMI patients and found IV morphine was significantly associated with higher mortality in NSTEMI patients after propensity score matched analysis. Likewise, in a 2017 study of 1740 NSTEMI patients, IV morphine was statistically significant for a larger infarct size and longer LOS after propensity score matching (McCarthy et al., 2017). Although morphine was not a significant predictor of infarct size or myocardial dysfunction in our study, it was borderline significant in both outcomes. With a larger sample size this may become significant. Given the controversial evidence, it is unclear whether the risk of morphine administration may exceed the benefits in NSTEMI patients. Further research including

randomized controlled trials that observe clinical outcomes is warranted before a clear conclusion or recommendation can be drawn.

6.4 LIMITATIONS

There were several limitations observed in our study. This study lacks power due to the small sample size and a nonrandomized model. With a larger sample size, other confounding variables can be controlled for which may lead to significant statistical results. Morphine dosage and timing was collected, however could not be included do to a large skew in data. Do to the chaotic and rushed environment in the ED, verbal order medications and a thorough history and physical were undocumented or underreported. Several patients received acute care in a UPMC affiliated ED while visiting Pittsburgh from other states. Their charts were unable to be accessed for the 30-day follow up data because the follow up data were inaccessible from another hospital system. Patients from this study were enrolled from 2012 to 2013, thus temporal changes in practice at UPMC emergency medicine may have occurred by the time these data were analyzed.

6.5 CONCLUSION

In this study, morphine use was not associated with infarct size, myocardial dysfunction, or MACE after controlling for MI type and other potential confounders. Pending undisputed evidence from randomized controlled trials, current guidelines should continue to be followed for the management of AMI patients. As more attention is drawn to this topic, there will be increasing

literature published. Future updates to recommended ACC/AHA AMI guidelines can be expected considering the recent trend of guideline publications over the past decade. It would behoove the nurses and other providers in the ED setting to be educated on this matter, in order to implement the best patient centered care and evidence-based practice.

Appendix A Results

Demographic and clinical characteristics of the study sample are found in Table 2. The regression models evaluating the predictors of each major clinical outcome in STEMI vs. NSTEMI are presented in Table 3 (infarct size), Table 4 (myocardial dysfunction), and Table 5 (30-day MACE).

Table 2: Demographic and Clinical Characteristics

Demographics	Morphine Administration (n=58)	No Morphine Administration (n=97)	P-Value
Age (years)±SD	61±18	66±14	**0.030**
BMI (kg/m2)±SD	31.2±8.5	29.6±6.8	0.190
Male	60%	58%	0.730
Black	36%	25%	0.148
Smoker	67%	57%	0.461
Medical History			
HTN	74%	70%	0.587
DM2	35%	31%	0.724
HLD	50%	54%	0.622
HF	19%	12%	0.237
CAD	45%	38%	0.400
Angina	19%	9.40%	0.136
Prior MI	28%	28%	0.940
PAD	9%	6%	0.748
Prior Stroke	8.50%	10.40%	0.339
Chronic Lung Disease	28%	21%	0.432
Prior PCI	29%	25%	0.577
Prior CABG	14%	14%	0.965
Vessel Occlusion			
LAD (%)±SD	81±21	75±27	0.269
LCx (%)±SD	68±28	66±27	0.743
RCA (%)±SD	75±30	76±30	0.905
Culprit Lesion			
LAD	41%	49%	0.406
LCx	19%	23%	0.686
RCA	36%	36%	0.975
Presenting Signs			
Cr median(25th-75th percentile)	1.0[0.8-1.2]	1.0[0.9-1.3]	0.175
Glucose (mg/dL)±SD	147±51	175±95	**0.019**
SOB	59%	52%	0.505
Diaphoresis	40%	46%	0.504
GI Upset	43%	47%	0.496
PH HR (beat/min)±SD	86±20	84±31	0.730
PH RR (Respirations/min)±SD	20±4	19±4	0.180
PH SaO2 (%)±SD	98±3	98±3	0.510
PH SBP (mmHg)±SD	144±36	146±43	0.830
PH DBP (mmHg)±SD	86±27	86±22	0.900
Pain (0-10)±SD	7.4±2.6	3.9±3.5	**<0.001**
Outcomes			
STEMI	58%	51%	0.503
LOS	3.0[2.3-5.2]	3.2[2.2-4.9]	0.581
Peak Troponin level	13.8(3.6-77.4)	7.9(1.3-29.2)	0.283
LVEF (%)±SD	50±13	52±11	0.465
30day MACE	28%	33%	0.290

Table 3: Univariate and Multivariate Predictors of Infarct Size

	STEMI (82)		NSTEMI (73)	
Predictors	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Demographics				
Age	NS	–	NS	–
Sex	NS	–	NS	–
Race	NS	–	NS	–
BMI	NS	–	NS	–
Smoking	NS	–	NS	–
Past Medical History				
HTN	NS	–	p = 0.080	**p = 0.037**
DM	NS	–	NS	–
Dyslipidemia	NS	–	NS	–
Known HF	NS	–	NS	–
CAD	NS	–	NS	–
Angina	NS	–	NS	–
Prior MI	NS	–	NS	–
PAD	NS	–	NS	–
Prior Stroke	NS	–	NS	–
Chronic Lung Disease	NS	–	NS	–
Prior PCI	NS	–	NS	–
Prior CABG	NS	–	NS	–
Clinical Presentation				
SOB	NS	–	NS	–
Diaphoresis	NS	–	NS	–
GI Upset	NS	–	NS	–
HR	NS	–	p = 0.049	p = 0.073
RR	NS	–	p = 0.034	**p = 0.048**
SBP	NS	–	NS	–
DBP	NS	–	NS	–
O2 Sat	NS	–	NS	–
Pain Score	NS	–	0.073	p = 0.284
Diagnostic Workup				
Glucose	NS	–	NS	–
Creatinine	NS	–	NS	–
LAD Occlusion	NS	–	NS	–
LCX Occlusion	NS	–	NS	–
RCA Occlusion	NS	–	NS	–
Initial Treatment				
Oxygen at the ED	NS	–	p = 0.002	**p = 0.002**
IV Morphine	NS	–	p = 0.086	p = 0.133

Table 4: Univariate and Multivariate Predictors of Myocardial Dysfunction

	STEMI (82)		NSTEMI (73)	
Predictors	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Demographics				
Age	NS	–	NS	–
Sex	p = 0.016	**p = 0.044**	NS	–
Race	NS	–	NS	–
BMI	NS	–	NS	–
Smoking	NS	–	NS	–
Past Medical History				
HTN	NS	–	NS	–
DM	NS	–	NS	–
Dyslipidemia	NS	–	p = 0.060	p = 0.084
Known HF	p = 0.013	**p = 0.014**	p = 0.052	p = 0.361
CAD	NS	–	NS	–
Angina	NS	–	NS	–
Prior MI	NS	–	NS	–
PAD	p = 0.071	p = 0.393	NS	–
Prior Stroke	NS	–	NS	–
Chronic Lung Disease	NS	–	NS	–
Prior PCI	NS	–	NS	–
Prior CABG	NS	–	NS	–
Clinical Presentation				
SOB	NS	–	p = 0.023	**p = 0.049**
Diaphoresis	NS	–	NS	–
GI Upset	NS	–	NS	–
HR	NS	–	NS	–
RR	NS	–	NS	–
SBP	NS	–	NS	–
DBP	NS	–	NS	–
O2 Sat	NS	–	NS	–
Pain Score	NS	–	NS	–
Diagnostic Workup				
Glucose	NS	–	NS	–
Creatinine	NS	–	NS	–
LAD Occlusion	p = 0.001	**p = 0.002**	NS	–
LCX Occlusion	NS	–	NS	–
RCA Occlusion	NS	–	NS	–
Initial Treatment				
Oxygen at the ED	NS	–	NS	–
IV Morphine	NS	–	p = 0.046	p = 0.084

Table 5: Univariate and Multivariate Predictors of 30-Day MACE

	STEMI (n=82)		NSTEMI (n=73)	
Predictors	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Demographics				
Age	NS	–	NS	–
Sex	NS	–	NS	–
Race	NS	–	NS	–
BMI	NS	–	NS	–
Smoking	NS	–	NS	–
Past Medical History				
HTN	NS	–	NS	–
DM	NS	–	NS	–
Dyslipidemia	NS	–	NS	–
Known HF	p = 0.034	p = 0.254	NS	–
CAD	NS	–	NS	–
Angina	NS	–	NS	–
Prior MI	NS	–	NS	–
PAD	NS	–	NS	–
Prior Stroke	NS	–	NS	–
Chronic Lung Disease	NS	–	NS	–
Prior PCI	NS	–	NS	–
Prior CABG	NS	–	p = 0.075	**p = 0.040**
Clinical Presentation				
SOB	NS	–	p = 0.112	p = 0.125
Diaphoresis	NS	–	NS	–
GI Upset	NS	–	NS	–
HR	NS	–	NS	–
RR	NS	–	NS	–
SBP	p = 0.007	**p = 0.041**	NS	–
DBP	NS	–	NS	–
O2 Sat	NS	–	NS	–
Pain Score	NS	–	NS	–
Diagnostic Workup				
Glucose	p = 0.016	p = 0.143	p = 0.051	**p = 0.029**
Creatinine	p = 0.011	**p = 0.017**	NS	–
LAD Occlusion	NS	–	NS	–
LCX Occlusion	NS	–	NS	–
RCA Occlusion	NS	–	NS	–
Initial Treatment				
Oxygen at the ED	NS	–	NS	–
IV Morphine	NS	–	NS	–

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