

Review Article

An Evidence-Based Review of Pain Management in Acute Myocardial Infarction

Abdikarim ABDI¹ and Bilgen Basgut^{1,2*}¹Department of Clinical Pharmacy, Near East University, Turkey²Department of Pharmacology, Near East University, Turkey

*Corresponding author

Bilgen Basgut, Department of Clinical Pharmacy and Pharmacology, Near East University, North Cyprus, Mersin10, Turkey, Email: bilgenbasgut@gmail.com

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Abstract

Since the turn of the twentieth century, morphine, an opioid analgesic, has played an integral role in the management of pain in myocardial infarction (MI). This is attributed to morphine's effect on reducing blood pressure, slowing heart rate, and relieving anxiety, which may decrease myocardial oxygen demand, added to the fact that morphine has been studied extensively in pain management in many settings. For this morphine kept considered amongst the first line therapies and most effective for acute pain management in MI patients according to many guidelines.

However, observational data suggest that morphine administration during acute myocardial infarction (AMI) may have negative consequences, while this practice also lacks supporting rigorous evidence or studies designed to assess the effect of morphine administration. Added to this recent evidence uncovered that morphine may impede gastrointestinal absorption of oral antiplatelet drugs important in reducing mortality in AMI.

These observations permit a comprehensive evaluation of the rationality of administration of morphine in AMI, and whether better alternatives are available in currently used analgesics or by using a morphine non-interacting P2Y12 receptor inhibitor for AMI patients.

In this review we discuss the rationality of morphine use according to recent evidence and the side effects and drug-drug interactions of morphine affecting MI patient with the present alternatives based on the findings of experimental, observational and randomized clinical studies.

INTRODUCTION

Myocardial infarction (MI) is a major cause of mortality and disability worldwide. The term MI reflects cell death of cardiac myocytes caused by ischemia, as a result of a perfusion imbalance between supply and demand. It's most obvious classical clinical symptoms include various combinations of chest, upper extremity, jaw, or epigastric discomfort on exertion or at rest [1]. The discomfort associated with acute myocardial infarction (AMI) usually lasts at least 20 minutes. Often, the discomfort is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnoea, diaphoresis, nausea, or syncope. Relief of stressful symptoms as chest pain is important, not only for patient well being, but also because stress induces systemic circulatory effect that may worsen the ongoing infarction [2].

Since 1923 when James MacKenzie first suggested use of morphine and chloroform for treating cardiac patients with bed rest until unconsciousness is achieved. Since then morphine has

been considered as one of the first line medications recommended for pain control in AMI. This was attributed to morphine effect on reducing blood pressure, slowing heart rate, and relieving anxiety, which may decrease myocardial oxygen demand, added to the fact that morphine has been studied extensively in pain management in many other settings while opioids are generally considered the first line therapies and most effective for acute pain management [2,3].

Despite this, morphine use in the setting of AMI lacks supporting rigorous evidence or studies designed to assess the effect of morphine administration. Yet many international guidelines such as the American College of Cardiology, the American Heart Association, and the European Society of Cardiology guidelines recommend morphine administration as a standard therapy in pain management in AMI [4,5].

Added to the critique of lack of strong evidence, a large observational study in 2005 reported that the use of morphine either alone or in combination with nitroglycerin was associated

with higher mortality than nitroglycerin alone, whereas new studies and trials may further explain this by associating morphine use with attenuation of action of oral antiplatelet medications [6,7].

These observations permit a comprehensive evaluation of the rationality of administration of morphine in AMI, how it impacts MI treatment and reperfusion therapy success, and whether better alternatives exist for managing pain in AMI patients, which warrant rigorously designed studies.

Ischemic pain of acute myocardial infarction

MI is defined as myocardial cell death due to prolonged ischemia. Coronary atherosclerosis is a chronic disease with stable and unstable periods. During unstable periods with activated inflammation in the vascular wall, patients may develop MI. The mechanism of MI often involves a complete blockage of a coronary artery or more caused by a rupture of an atherosclerotic plaque or less commonly due to coronary artery spasms.

Due to the myocardial cell death or ischemia, MI is most commonly accompanied by chest pain, tightness or discomfort which may radiate to shoulders, arms, back, neck, or jaw. This pain together with blood flow abnormalities, induce a massive surge of catecholamine release from the sympathetic nervous system leading to systemic circulatory effects such as an increase in blood pressure, heart rate, and stroke volume. As a result these changes may adversely further influence the balance between myocardial metabolic requirement and supply and further result in infarct extension [8,9].

The amount of myocardium that undergoes necrosis in MI is an important predictor of morbidity and mortality. The infarction does not occur instantaneously, it first develops in the subendocardium and progresses as a wave-front of necrosis from subendocardium to subepicardium over the course of several hours. Transient coronary occlusion may cause only subendocardial necrosis, whereas persistent occlusion eventually leads to transmural necrosis. The goal of acute coronary interventions generally is to interrupt this wave-front and limit myocardial necrosis [10].

Restoration of arterial blood flow remains the only way to salvage ischemic myocytes permanently, by either thrombolytic enzymes or percutaneous coronary intervention (PCI) or by Coronary artery bypass grafting (CABG), in addition to the following interventions that can delay ischemic injury which include oxygen, nitroglycerine, thrombolytic agents, β -blockers, and pain management [9,10].

Concerns around morphine use

Beside the effectiveness of morphine in management of pain and its clinical use to relieve chest pain in AMI; a practice first documented back in 1912, and since then been the ultimate practice supported with major therapy guidelines till today [11]. However strong criticisms to its use exist.

To start with, there have never been any randomized, controlled, clinical trials or large scale observations evaluating and supporting the efficacy or safety of morphine for use in ACS

while many guideline recommendations were not based upon randomized clinical trials but only upon expert opinion which is considered to be "poor" form of evidence.

Secondly morphine known side effects such as hypotension, bradycardia and respiratory depression, may result in deleterious outcomes in high doses especially in AMI patients who might lack the coronary reserve required to withstand the stresses of hypotension and hypoxemia [12-17].

The CRUSADE registry which is a retrospective, observational study of 57 000 patients in which a total of 17,003 patients (29.8%) received morphine within 24 hours of presentation, revealed that administration of morphine either alone or in combination with nitroglycerin was associated with higher mortality for patients presenting with non-ST-segment elevation myocardial infarction (NSTEMI) [6].

This analysis raised concerns regarding the safety of using morphine in patients with NSTEMI and emphasized on the need for randomized trials.

This outcome of morphine administration could be due to morphine effect of blunting the severity of angina without actually ameliorating the underlying pathophysiologic cause of chest pain (i.e., coronary hypoperfusion) or due to morphine effect on oral antiplatelet drugs absorption as shown in later studies [6].

In contrast a second observational study was carried, aiming to assess the potential clinical impact of pre-hospital morphine administration in ST-elevation myocardial infarction (STEMI) patients from a nationwide French registry. 4,169 patients with AMI were included 19% of them received morphine during pre-hospital management, and the study concluded that pre-hospital morphine use was not associated with an increase of in-hospital complication and one-year mortality; and, could be more used as recommended in the guidelines. [18].

In animal studies, morphine has been demonstrated quite conclusively to increase myocardial infarction size as reported by Markiewicz W. et al., 1982 [19] while contradictory to these results, several other studies found morphine and particularly selective delta receptor's opioid agonists to show powerful cardioprotective effects in numerous animal models and man where in low doses it triggers a powerful endogenous system that leads to a marked reduction in infarct size, called the phenomenon of ischemic preconditioning [20,21].

So to develop a clear cause effect relationship, randomized controlled clinical trials are necessary and warranted. As recent trials uncovered a very important effect associated with morphine use in MI that was not been noticed for the last decades (Table 1).

Recently in 2013 Parodi and his colleagues while studying prasugrel and ticagrelor loading doses in STEMI patients observed that the onset of action of prasugrel and ticagrelor was delayed by co-administration of morphine as a result of a drug-to-drug interaction (DDI) [22-24].

Later in the ATLANTIC study, in-ambulance administration of ticagrelor in patients with STEMI transferred for primary PCI, improved coronary reperfusion only in those patient groups who did not receive morphine. [25].

Table 1: Studies regarding outcomes of morphine administration in AMI.

Authors / year	Study name	Study Design	Study Aim	Population	Results
Thomas, Michael, et al; 1965 [12]	Haemodynamic effects of morphine in patients with acute myocardial infarction	Prospective clinical trail	Haemodynamic effects of morphine in patients with acute myocardial infarction	N=13 AMI patients	Morphine associated with haemodynamic instability such as hypotension, bradycardia and respiratory depression.
Meine, Trip J., et al; 2005 [6]	"Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative."	retrospective, observational registry enrolling patients	evaluate the use of morphine within the first 24 hours after presentation in patients	N=57039 NSTEMI	Morphine associated with negative impact on mortality and clinical outcome.
Iakobishvili Z, et al; 2010 [83]	Effect of Narcotic Treatment on Outcomes of Acute Coronary Syndromes : (ACSIS) 2008 database	Retrospective, observational registry, focused on morphine.	Evaluation of the effect of prehospital and in-hospital IV narcotics use on the in-hospital and 30-day outcomes among consecutive patients with various types of ACS.	n = 765 STEMI n = 993 NSTEMI	Neutral regarding clinical outcome
Puymirat, Etienne, et al ; 2015 [18]	Correlates of pre-hospital morphine use in ST-elevation myocardial infarction patients and its association with in-hospital outcomes and long-term mortality: the FAST-MI (French Registry of STEMI & NSTEMI) programme.	retrospective, observational registry	the potential clinical impact of pre-hospital morphine administration in STEMI patients	N= 4,169 19% (792) on morphine	Pre-hospital morphine use was not associated with an increase of in-hospital complication and one-year mortality.
De Waha, Suzanne, et al.; 2015 [27]	Intravenous morphine administration and reperfusion success in ST-elevation myocardial infarction: insights from cardiac magnetic resonance imaging.	Observational, focused on morphine.	To analyze the impact of IV morphine on ischemic injury and salvaged myocardium assessed by cardiac magnetic resonance imaging in patients with STEMI reperfused by PPCI.	n = 276 STEMI	Suspected negative impact on clinical surrogate end-point.

The first randomized, double-blind, placebo-controlled, cross-over trial was carried in 2014 by Eva-Luise Hobl and her colleagues to examine the possible drug–drug interactions between clopidogrel and morphine. They found that morphine delays clopidogrel absorption, decreases plasma levels of clopidogrel active metabolite, and retards and diminishes its effects, which may lead to treatment failure in susceptible individuals [7].

Further in a second trial, the IMPRESSION trial was performed in 70 patients (35 in each study group) in a single-centre. The study also found that morphine delays and attenuates ticagrelor exposure and action in patients with MI [26].

Other researchers also recently found that IV morphine administration prior to PCI to be independently associated with suboptimal reperfusion success after PCI in patients with STEMI [27].

Mechanisms and hypothesis behind morphine associated negative outcomes

In patients with MI, a number of medications of importance in terms of mortality and morbidity are usually administered all together, thereby raising the potential risk for drug-to-drug interaction. As our knowledge of the morphine–antiplatelet interaction has increased significantly over the last 3 years, recent evidence may explain morphine administration associated negative outcomes in AMI patients [6,28].

Drug interactions can occur due to pharmacokinetic interactions including rate of absorption, metabolic pathways, drug transport through membranes and protein binding. While opioids provide highly effective pain relief, the therapeutic activity of opioids is compromised by their gastrointestinal adverse profile. Opioids slow gastrointestinal tract motility and decrease intestinal secretions both by a central nervous system-mediated effect and an effect on the peripheral opioid receptors in the GI tract. As this may induce also nausea and vomiting; a well-known opioid-induced effects, it is also hypothesized that low doses of opioids activate mu opioid receptors in the chemoreceptor trigger zone (CTZ), thereby stimulating further vomiting [29].

Opioid-induced bowel dysfunction is also another adverse effect, which in turn reduce or delay absorption and decrease peak plasma drug concentration levels (i.e. C_{max}) of other orally administered drugs [30].

Opioids such as methadone were early reported to affect absorption of antiviral drugs as an example, by increasing their exposure to inactivating gastric acids and by this decreasing their bioavailability [7]. In the case of morphine in AMI, as reported by Eva-Luise Hobl and her colleagues, morphine injection delayed maximal plasma concentrations of clopidogrel (T_{max} : 105 vs. 83 min, $p = 0.025$) and reduced both the C_{max} of clopidogrel active metabolite (from 171 to 113 ng/ml, $p = 0.025$) and the total exposure as measured by the AUC_{0-n} by 34% (16,840 vs. 11,103 ng x h/ml, $p = 0.001$). As a result morphine administration delayed clopidogrel absorption ($p = 0.025$) and delayed the maximal

inhibition of platelet aggregation on average by 2 h (n = 24; p < 0.001). Residual platelet aggregation was higher 1 to 4 h after morphine injection (n = 24; p < 0.005). Furthermore, morphine delayed the inhibition of platelet plug formation under high shear rates (P2Y-Innovance; n = 21; p < 0.004) and abolished the 3-fold prolongation in collagen adenosine diphosphate induced closure times seen in extensive and rapid metabolizers (n = 16; p = 0.001) [26].

Meanwhile Jacek Kubica et al reported from the IMPRESSION trial that morphine also delay and attenuate ticagrelor exposure and action in patients with MI by 36% decrease in exposure (AUC(0 - 12): 6307 vs. 9791 ng h/mL; P = 0.003), and 37% (AUC(0 - 12): 1503 vs. 2388 ng h/mL; P = 0.008), respectively, with a concomitant delay in maximal plasma concentration of ticagrelor (4 vs. 2 h; P = 0.004) [24,26].

Multiple regression analysis of the IMPRESSION trial showed that lower AUC(0 - 12) values for ticagrelor were independently associated with the administration of morphine (P = 0.004) and the presence of STEMI (P = 0.014). While All three methods of platelet reactivity assessment carried in this study showed a stronger antiplatelet effect in the placebo group and a greater prevalence of high platelet reactivity in patients receiving morphine. Morphine was also concluded not to affect conversion of ticagrelor to its active metabolite in AMI patients [26].

These effects of morphine on plasma concentration levels of oral antiplatelet medications are hypothetically attributed to decreased concentrations of the parent compound, probably resulting from morphine-induced impaired gastric emptying, lower intestinal motility and higher incidence of vomiting [28].

It is also hypothesized that patients who received morphine might be subjects at higher risk of negative outcomes. Thus, it is possible that in sicker patients, haemodynamic derangement, adrenergic activation, and systemic vasoconstriction with the reduction of blood volume to the abdomen may contribute to the delayed drug adsorption and to the reduced platelet inhibition. But the same morphine effect was also reported from the IMPRESSION trial in healthy subjects [26].

Potent P2Y12-inhibitors (prasugrel and ticagrelor) were hypothesized to provide an effective alternative to clopidogrel when morphine is given, but in a later multicentre study the drug-to-drug interaction between morphine and antiplatelet agents was observed in 300 STEMI patients undergoing PCI receiving either prasugrel and ticagrelor. This association persisted even after excluding patients who vomitted [31].

Cortisol, or hydrocortisone, is a steroid hormone (glucocorticoid) that is vital to the endocrine system released by the adrenal cortex to combat stress, opioid are well known for their effect of inducing cortisol deficiency which may advance to episodes of Addisonian crises [32]. Symptoms include gastrointestinal effects, extreme weakness, mental confusion, darkening of the skin, dizziness, nausea or abdominal pain, vomiting and fever, though all dont appear spontaneously. A single 5-mg intravenous dose of morphine sulfate quickly paralyzes cortisol production in opioid-naive men and women, with a drop of more than 75% from baseline within

3 hours [33,34]. A meta-analysis of 11 trials (2,646 patients) suggests a possible mortality decrease with corticosteroids. Additional studies examining the effectiveness of replacement corticosteroids, perhaps beginning concurrently with morphine administration in patients with AMIs, are also warranted [35].

Other mechanisms that may result in the negative outcomes associated with morphine administration in AMI, include decrease in myocardial oxygen delivery, decrease of arterial oxygenation, increase in arterial carbon dioxide, and perhaps even cerebral hypoperfusion [36].

Suggested alternatives for analgesia in acute MI

Oral antiplatelet agents are the mainstay of pharmacological treatment in patients with MI, while 30 % of these patients are co-prescribed morphine which affects the absorption of the first. Thus its of importance to review guidelines and further charectorize and develop strategies to overcome this interaction which could lead to treatment failure in susceptible patients.

In the following paragraphs we address the possible alternatives and management of morphine antiplatelet interaction [37,38].

Non-steroidal antiinflammatory drugs (NSAIDs)

Ketorolac and indoprofen were amongst the earliest Non steroidal Antiinflammatory drugs (NSAIDs) analgesics suggesting for pain management in MI [39,40]. NSAIDs are a group of agents widely used for their anti-inflammatory, antipyretics, and analgesics. Their main mechanism of action is to inhibit a class of enzymes known as cyclooxygenases (COX-1 & COX-2). According to the isoenzyme they preferentially block, traditionally, they are devided into COX-1 inhibitors which are very few with aspirin the most commonly used, COX-2 inhibitors which include rofecoxib, celecoxib, valdecoxib, parecoxib, etoricoxib, and lumaricoxib, and non selective NSAIDs, which inhibit both COX-1 and COX-2 indiscriminately, and include diclofenac, naproxen, ibuprofen, indomethacin, and piroxicam [41-44].

NSAIDs offer effective pain relief for the most common forms of pain both acute and chronic ones, and are thus widely used for relief of pain for a wide range of medical conditions (44), but despite their widespread use, the US Food and Drug Administration (FDA) in July 2015 strengthened warnings about the risk of heart attack and stroke associated with nonsteroidal antiinflammatory drugs (NSAIDs) [45]. The relationship between NSAID use and cardiovascular events has long been subject to numerous observational studies, clinical trials and meta-analyses, with sometimes ambiguous conclusions [46,47].

The increased risk for cardiovascular events was first demonstrated for COX-2 inhibitors but later found also associated with most NSAIDs. A meta-analysis in 2006, of 138 randomized trials was done in comparing the risk of vascular events of COX-2 inhibitors and traditional NSAIDs on 145,373 enrolled patients. The analysis found COX-2 inhibitors as well as high-dose diclofenac and ibuprofen to be associated with a higher risk of vascular events, mainly MI, in contrast to high-dose naproxen [48].

In a systematic review of community-based controlled observational studies published 2011, the aim was to provide estimates of the comparative risks with individual NSAIDs at typical doses. The review included data from 21 cohort studies with 2.7 million exposed individuals and 30 case–controls, with a total of 184,946 cardiovascular events. The highest overall cardiovascular risks were seen with rofecoxib and diclofenac, while the lowest with low dose ibuprofen and naproxen [49]. Naproxen was reported also from a meta-analysis of 31 large-scale randomized trials, **to be least harmful compared to other NSAIDs and not being associated with MI or cardiovascular death** [50].

A large LANCET published meta-analysis came by in 2013, aimed to characterize vascular and gastrointestinal effects of NSAIDs, particularly in patients at increased risk of vascular disease. The review concluded that the vascular risks of high-dose diclofenac, and possibly ibuprofen, were comparable to COX-2 inhibitors, whereas high-dose naproxen was associated with less vascular risk than other NSAIDs [51,52].

It is thought that NSAIDs increased cardiovascular risk is due to either “platelet COX-1 to endothelial COX-2 inhibition imbalance”, or to chronic renal COX-2 inhibition resulting in hypertension, or both together. In the first case risk would be immediate, in the second it would be time-dependent.

Also naproxen, ibuprofen and other NSAIDs may inhibit the cardioprotection of aspirin when administered in close time proximity with it. Bleeding is a concern too, coadministration of antithrombotic treatments with all types of NSAIDs (except aspirin) has been shown to increase the bleeding risk in patients with MI [53,54].

Though the time course of the risk has not been clearly elucidated, with arguments for an association with prolonged duration of use only. Few evidence suggest NSAIDs to be considered relatively safe drugs when prescribed at the most effective dose and for the shortest duration of time, which was defined to be 10 days or fewer in some studies, while others studies indicate constant risk with also short term use of NSAIDs [47,51].

For this though it may sound reasonable out of all NSAIDs to evaluate short term naproxen (the least risky NSAID) compared to narcotics for acute analgesia in MI patients, as some NSAIDs shown to give better pain relief than morphine [46,47]. The FDA Advisory Committee went to that current data does not support the conclusion that naproxen has a lower risk of thrombotic events than other NSAIDs; and that there is no latency period for the risk of cardiovascular thrombotic events is associated with NSAID use [46].

Hence NSAIDs though being effective analgesic agents, their use is attenuated due to their associated cardiovascular events risk and thus cannot be considered as alternatives for opioids till new supporting evidence emerges, while The only NSAID drug that should be given to such a patient before ACS has been definitely ruled out is aspirin [55].

Five alternative strategies for analgesia in AMI

IV nitrates and Beta-blockers: As Ischemia being the main

etiology behind chest pain in AMI, reperfusion therapy in STEMI and high risk NSTEMI patients is the most important component of treatment, which strongly influences short- and long-term patient outcomes.

In mild NSTEMI patients, immediate relief of ischemia and prevention of recurrent MI and death is achieved with proper antianginal, antiplatelet, and anticoagulant therapy. Of these nitrates and beta-blockers (BBs) achieve a rapid reduction of pain intensity [56,57].

It is reasonable to administer intravenous BBs at the time of presentation to patients with STEMI who are hypertensive or have an ongoing ischemia and no contraindications to beta blockers use [5]. Early intravenous metoprolol followed by high-dose oral therapy had a neutral effect on the combined endpoint of death, recurrent MI, or cardiac arrest. There were lower rates of recurrent MI and ventricular fibrillation (VF) in the treated groups, but with a significantly higher rate of cardiogenic shock with metoprolol, especially on days 0 and 1 [5].

A Meta-analysis of randomized trials enrolling at least 100 patients was carried to evaluate BBs use in MI. Sixty trials with 102,003 patients were eligible, BBs reduced mortality in studies carried before widely adopting the reperfusion therapy, but not in the reperfusion era. In contemporary practice of treatment of MI, BBs have no mortality benefit but reduce recurrent MI and angina (short-term) at the expense of increase in heart failure, cardiogenic shock and drug discontinuation. Current guidelines recommend as a class 2 recommendations to administer intravenous BBs at the time of presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia [5].

Nitrates are recommended for the relief of chest pain in both AHA and ESC guidelines. They work by reducing LV preload and increasing coronary blood flow which results in a decrease in myocardial oxygen consumption and thus relieve the symptoms of ischemia. But in clinical practice it does not affect the myocardial injury unless a significant vasospasm is present [5,56].

Guidelines recommendations are mainly attributed to preperfusion era trials which reported some beneficial effect on mortality [58]. Also a retrospective study of 8,255 patients of whom 1,662 (20%) received sublingual NTG, revealed that the chest pain score (on a scale of 0–10) after receiving NTG decreased from 6.9 to 4.4 (a mean difference of 2.5; 95% confidence limit 2.4–2.8) [59].

In contrast to this a recent multicenter randomized controlled trial reported that Sodium nitrite administered intravenously immediately prior to reperfusion in patients with STEMI does not reduce infarct size [60].

Thus we conclude from these evidence that nitrates can ameliorate symptoms and signs of myocardial ischemia, whilst they could be useful in absence of contraindications especially in patients with persistent ischemia and concomitant hypertension or heart failure [5,56].

IV Acetaminophen, still the safest Analgesic: Acetaminophen (APAP) or Paracetamol, has been a mainstay for pain and fever management for many years. Its has been used for decades ef-

fectively for the management of mild to moderate pain. its IV formulation have been widely used in Europe since 2 decades and is proposed for pain of sudden onset in people in the emergency department though not sufficiently studied yet [61,62].

Parodi proposed the use of IV paracetamol in AMI. APAP is highly safe and preferred in pain management particularly in those with increased cardiovascular risk or kidney disease, unlike NSAIDs [53]. Fourteen randomized controlled trials were recently identified in MEDLINE and EMBASE, they had various methodologic flaws, and the studies enrolled a sum of 1,472 patients.

In 8 of the fourteen trials IV APAP was reported to be comparable with other pain medications with no statistical difference in pain score, the medications compared included different effective doses of morphine, oxycodone, tramadol, piroxicam, topical 5% lidocaine and dexketoprofen.

In the other studies, IV APAP was reported to be superior compared to IV morphine and IM piroxicam, where it was associated with significant reduction in pain scores. While the incidence of side effects associated with IV APAP was very low. A limitation to generalising these results is the fact that the level of evidence for the individual trials ranged from very low to moderate and thus limited evidence to support the use of APAP for acute pain control in ED with "no studies" being yet done in AMI patients [63].

Opiates May All be Equal, but They Are Not All the Same:

Opioids have similar properties to the opium from which they are derived, while they target the same endorphin receptor, but still they have many differences pharmacologically, experimentally, clinically and from health economics point of view [64]. The short acting synthetic opioid alfentanil is commonly used in anaesthesia, it favoring characteristics include its rapid onset of action, of 1–2 minutes shown to be safe also for cardiac patients, and better side effects profile than morphine (more controllable due short duration of action). Furthermore, alfentanil seems to liberate less histamine than morphine, which is hypothesized to have a role in GI side effects of morphine including delayed motility and thus alfentanil may less interact with oral antiplatelet therapies [65-67].

A randomised double-blind clinical trial in which the effects of alfentanil were compared with those of morphine in the prehospital treatment of 40 haemodynamically stable patients suffering from acute ischaemic-type chest pain. The study reported that pain relief was faster ($p < 0.005$) in the alfentanil group than in the morphine group. Alfentanil provided effective analgesia during the follow-up period of 15 minutes with no haemodynamic or respiratory side effects.

The study concluded that alfentanil is an effective analgesic in the prehospital treatment of myocardial ischaemic pain. Intranasal fentanyl also showed in another RCT to have no significant difference in analgesia compared with intravenous morphine for prehospital analgesia [67,68]. Nevertheless further RCT are necessary to exclude or verify the magnitude of interaction of Alfentanil if it occurs.

Tramadol was also shown to have a significant effect on gastric emptying which is measurable but smaller than morphine and may thus have clinical and economic advantages in acute pain management compared with morphine [69].

Tramadol has been in clinical use in Germany since the late 1970s and has proven effective in both experimental and clinical pain without causing serious cardiovascular or respiratory side effects. Its proposed for firstline management of postoperative pain instead of morphine. It is also associated with a low incidence of cardiac depression and significantly less dizziness and drowsiness than morphine [70,71].

In contrast to morphine, tramadol has not been shown to induce histamine release. At therapeutic doses, tramadol has no effect on heart rate, left ventricular function or cardiac index [72].

Tapentadol is also an orally active, centrally acting synthetic analgesic that is thought to exert its analgesic effects as tramadol via a dual mechanisms of action (μ opioid receptor agonism and norepinephrine reuptake inhibition). Tapentadol offers also the prospect of reduced opioid-related gastrointestinal adverse events and hence do not significantly increase the possibility of delayed absorption of other drugs while maintaining adequate analgesia [73,74].

Combinations .. More effective but less toxic:

Tramadol As being effective in moderate to severe pain, while morphine is thought to be more effective for severe acute pain a combination drug containing tramadol hydrochloride 37.5 mg and acetaminophen 325 mg may reasonably reduce the onset time of analgesia and improves the degree of analgesia. The combination could be studied in AMI as this product reduces the incidence of tramadol related adverse events, while the addition of acetaminophen improves pain relief and provides a faster onset and longer duration of action with fewer adverse events than either component separately [73].

Also Opioid-induced bowel dysfunction and effects on other drugs can be effectively treated by combining morphine with a peripherally acting opioid receptor antagonists. Examples include oral naloxone or subcutaneous methylnaltrexone, such a combination could lead to less peripheral side effects of morphine and thus may favorably attenuate morphine's delayed absorption of oral antiplatelet medications [75,76].

Alternative Routes for P2Y12 receptor inhibitors:

Antiplatelet agents are the mainstay of pharmacological treatment in patients presenting with an AMI, the novel and potentially relevant drug-drug interaction (DDI) between morphine and oral P2Y12 receptor inhibitors indicate that co-administration of morphine should be avoided, if possible. As the DDI being mainly attributed to morphine delay effect of oral absorption of P2Y12 receptor inhibitors, crushing prasugrel and ticagrelor tablets may result in a better pharmacokinetic as was reported of crushed clopidogrel in a healthy volunteers study. 300 mg clopidogrel was administered and crushed via a nasogastric tube this resulted in a faster and greater bioavailability of the drug compared with whole tablets [77]. The same results were reported from The MOJITO (Mashed Or Just Integral pill of TicagrelOr) study [78]. The study revealed that crushed ticagrelor tablet administration in STEMI patients was feasible and provides earlier platelet

inhibition compared with standard integral tablets.

Also a study assessing STEMI patients undergoing PPCI (n = 52) who were treated with a prasugrel 60-mg loading dose (LD) either as whole or crushed tablets. PK/PD analyses were performed at 7 time points. The study revealed crushed prasugrel to lead to faster drug absorption, and consequently, more prompt and potent antiplatelet effects compared with whole tablet ingestion. Although the use of morphine was numerically higher in the crushed group, this did not reach statistical significance. Also morphine was used in though in 75% of the overall study population and was not associated with any significant difference on the primary endpoint. As well as during the overall 24-hours of study time course, there was no treatment effect by morphine interaction. Except that it was associated with modestly reduced exposure to prasugrel active metabolite but not a pharmacodynamic effect. This may suggest that beside the DDI other mechanisms may play a major role in the pathophysiology of delayed absorption of P2Y12 receptor inhibitors in patients undergoing PCI [79,80].

Cangrelor, an intravenous direct-acting P2Y12 receptor inhibitor, could be an ideal choice in patients with STEMI receiving morphine. As it is difficult to achieve adequate platelet inhibition at the time of PCI with oral agents due absorption delay that affect the onset of effect of antiplatelet, IV Cangrelor optimize treatment because it produces nearly maximal inhibition of platelet aggregation within minutes [81].

It also of mentioning that newer P2Y12 receptor inhibitor use is associated with a considerable economic burden on some patients in comparison to generic clopidogrel which also worth to be considered for cost effectiveness evaluation [82] (Table 2).

CONCLUSION

Almost for a century morphine, an opioid analgesic, had been the ultimate and most effective management of chest pain in AMI. Benefits were attributed to its lowering blood pressure, heart rate and alleviating anxiety, as it is also reported to exert cardioprotective effects, but still their use lacks supporting rigorous evidence examining long term outcomes.

The CRUSADE study raised concerns regarding the safety of using morphine in patients with NSTEMI ACS emphasizing the need for a randomized trials, smaller observations reported neutral effect of morphine. While pharmacodynamic observations published in 2013 suggested that the onset of action of prasugrel and ticagrelor may be delayed by co-administration of morphine, Morphine-P2Y12 inhibitors DDI was later confirmed by small RCTs.

The interaction is mainly due Morphine effect of delaying gastrointestinal motility and thus delaying the absorption of oral antiplatelets. Other hypothesized theories include, that morphine sulfate quickly paralyzes cortisol production in opioid-naive men and women, whilst scientists linked morphine effects to its histamine releasing effect.

Table 2: Studies regarding antiplatelet use in AMI and effect of morphine.

Authors / year	Study name	Study Design	Study Aim	Population	Results
Zafar, M. Urooj, et al; 2009 [77]	Crushed Clopidogrel Administered via Nasogastric Tube Has Faster and Greater Absorption than Oral Whole Tablets	A prospective open-label crossover clinical trial	To compare the absorption of 300 mg clopidogrel administered crushed via nasogastric (NG) tube versus whole tablets taken orally in healthy volunteers.	N= 9 healthy subjects	A 300 mg loading dose of crushed clopidogrel administered via NG tube provides faster and greater bioavailability than an equal dose taken orally as whole tablets
Parodi, Guido, et al.; 2013 [22]	Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study.	a randomized, 2-arm, prospective study	To evaluate the impact of increased ticagrelor LD on platelet inhibition as compared with the standard prasugrel LD.	n = 50 STEMI	Morphine use is associated with a delayed activity of ticagrelor and prasugrel
Morton, Allison C., et al; 2013 [85]	Morphine delays the onset of action of prasugrel in patients with prior history of STEMI	an open-label, crossover study	To determine whether morphine delays the onset of action of prasugrel in patients with previous PPCI for STEMI.	n = 11 post-STEMI	Negative impact on pharmacodynamics of prasugrel.
Hobl EL et al ; 2014 [7]	Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial	a randomized, double-blind, controlled trial	To examine possible drug-drug interaction between clopidogrel and morphine	n = 24 healthy subjects	Negative impact on pharmacokinetics and pharmacodynamics of clopidogrel
Parodi, Guido, et al.; 2015 [25]	Morphine Is Associated With a Delayed Activity of Oral Antiplatelet Agents in Patients With STEMI Undergoing Primary Percutaneous Coronary Intervention	patient-level integrated analysis from 5 studies	To assess platelet inhibition after a loading dose of the antiplatelet agents in STEMI patients according to morphine use.	n = 300 STEMI 32% (95 patients) on morphine	Morphine use is associated with a delayed onset of action of the oral antiplatelet agents. Even after excluding vomiting patients.

Franchi, Francesco, et al; 2015 [86]	Impact of morphine on pharmacokinetic and pharmacodynamic profiles of ticagrelor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.	a post-hoc analysis of a randomized study	To assess the impact of morphine on pharmacokinetic profiles of ticagrelor.	n = 46 AMI, 35% on morphine (16 patients)	use of morphine alters PK profile and delays the PD effects of ticagrelor
Silvain J et al ; 2015 [25]	Impact of morphine administration on ticagrelor-induced platelet inhibition in ST-elevation myocardial infarction patients treated by primary pci: results from the PRIVATE-ATLANTIC study	A sub analysis for randomized double blind placebo controlled trial	to assess the pharmacodynamic (PD) and pharmacokinetic (PK) effect of ticagrelor pretreatment.	n = 37 STEMI	Suspected negative impact on pharmacodynamics of ticagrelor.
Kubica J et al ; 2015 [26]	Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial	a single-centre, randomized, double-blind trial	To assess the influence of IV morphine on the pharmacokinetics and pharmacodynamics of ticagrelor and its active metabolite in AMI patients	n = 70 AMI	Morphine delays and attenuates ticagrelor exposure (PK) and action (PD) in patients with myocardial infarction
Hobl EL et al ; 2015 [80]	Morphine interaction with prasugrel: a double-blind, cross-over trial in healthy volunteers	randomized, double-blind, placebo-controlled, cross-over trial	To clarify whether more potent P2Y12-inhibitors may provide an effective alternative, we examined drug-drug interactions between morphine and prasugrel.	n = 12 healthy subjects	Negative impact on pharmacokinetics and neutral on pharmacodynamics of prasugrel.
Parodi, Guido, et al; 2015 [78]	Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study.	a prospective, 4-center, international, randomized, active-controlled study	to evaluate the superiority of ticagrelor crushed pills versus integral tablets of equal dose in STEMI patients	n= 82	crushed ticagrelor tablet administration in STEMI patients is feasible and provides earlier platelet inhibition compared with standard integral tablets
Hobl EL et al ; 2016 [87]	Morphine decreases ticagrelor concentrations but not its antiplatelet effects: a randomized trial in healthy volunteers	randomized, double-blind, controlled, crossover trial	to evaluate the effects of morphine on the intestinal resorption, pharmacokinetics and pharmacodynamics of ticagrelor	n = 24 healthy subjects	Morphine co-administration moderately decreases ticagrelor plasma concentrations but does not inhibit its pharmacodynamic effects
Rollini, Fabiana, et al; 2016 [79]	Crushed prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary intervention: the CRUSH study.	prospective, randomize, open-label study	to determine whether crushing prasugrel is associated with more favorable drug bioavailability and platelet inhibitory effects compared with whole tablets in STEMI patients undergoing PPCI.	n = 52	<ul style="list-style-type: none"> Crushed prasugrel leads to faster absorption, and more potent antiplatelet effects. Morphine wasn't associated with any significant difference on the primary endpoint. Morphine was associated with modestly reduced exposure to prasugrel active metabolite but not a pharmacodynamic effect in the uncrushed formulation group.

In search for alternatives for morphine in AMI, NSAIDs though being effective analgesic agents, their use is attenuated due to their associated cardiovascular events risk, while naproxen was reported to have minimum risk especially when administered for a short duration <10 days though still it may inhibit the cardioprotection of aspirin and thus strictly not recommended till supporting evidence emerges.

blockers and nitrates at the time of presentation to MI patients with no contraindications, which may lead to significant pain relief. Other alternatives as IV acetaminophen, was shown in small studies to be at least as equally effective as other analgesics, also its combination with tramadol could be effective for moderate to severe pain, as well as afentanyl, though all are not studied yet for interaction with antiplatelets and use in AMI.

It's reasonable to initially administer intravenous beta

Modifying route of administration of antiplatelets is also

an alternative associated with better pharmacokinetic profile for P2Y12 inhibitors, but not a pharmacodynamic effect when coadministered with morphine suggesting that other mechanisms may affect the pathophysiology of delayed absorption of P2Y12 inhibitors, which needs further rigorous evaluation.

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