Heart, Lung and Circulation (2019) **28,** 697–706
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.12.015

REVIEW

Opioids and ST Elevation Myocardial Infarction: A Systematic Review

Ji Quan Samuel Koh, MBBS [a,1], Himawan Fernando, MBBS [a,b,c,1], Karlheinz Peter, MD, PhD [a,c], Dion Stub, MBBS, PhD [a,b,c,d,e*]

[a]Alfred Hospital, Melbourne, Vic, Australia
[b]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Vic, Australia
[c]Baker IDI Heart and Diabetes Institute, Melbourne, Vic, Australia
[d]Western Health, Melbourne, Vic, Australia
[e]Ambulance Victoria, Melbourne, Vic, Australia

Received 12 July 2018; received in revised form 18 November 2018; accepted 20 December 2018; online published-ahead-of-print 1 February 2019

Background Traditionally, opioids have been the analgesia of choice for patients with ST-Elevation Myocardial Infarction (STEMI). Recent studies, however, have raised the possibility of harmful effects of opioid administration through delayed onset of antiplatelet agents.

Objective To perform a systematic review of the effects of parenteral opioids in patients presenting with STEMI.

Methods Medical databases were systematically searched to 28 February 2018. Randomised control trials (RCTs) and observational studies were included if they interrogated the effects of parenteral opioids as compared to no opioid administration in STEMI patients. Outcomes included in-hospital, 30-day, one-year major adverse cardiac events (MACE) and platelet reactivity measures. The studies were evaluated using GRADE (Grade of Recommendation, Assessment, Development and Evaluation).

Results One (1) RCT and 17 non-randomised, non-controlled observational studies were identified. The only RCT was of high quality, but only evaluated the pharmacokinetics of STEMI patients and had a small sample size. The remaining studies were of low-moderate quality, mainly due to eligibility criteria and confounding. Most studies report higher platelet reactivity with opioids, but clinical outcomes (MACE) were equivocal.

Conclusion This systematic review highlights the paucity of quality research evaluating the effect of opioids on its clinical and pharmacological effect on STEMI patients. Current literature indicates that opioids are associated with prolonged platelet reactivity. Whether this affects clinical outcomes remains to be established. Given the widespread use of opioids in STEMI, there is an urgent need for adequately powered trials investigating their safety.

Keywords Opioid • STEMI • Systematic review

Introduction

While bed rest and chloroform have been eliminated from century old practices in the management of ST-elevation myocardial infarction (STEMI) [1], opioids have remained an integral part of analgesia in emergent STEMI management to this day. The suggested theoretical benefits of opioids in STEMI are three-fold. Firstly, there is symptomatic relief through its analgesic properties. Secondly, with the reduction of pain, there is a potential physiological reduction in sympathetic response, resulting in a decrease in systemic vascular resistance and heart rate, which serves to equilibrate

*Corresponding author at: Alfred Hospital, Commercial Rd, Melbourne 3004, Australia. Tel. +61 9076 2000, Email: d.stub@alfred.org.au

[1] Dr Koh and Dr Fernando are co-first authors and contributed equally to the manuscript.

myocardial metabolic requirement and supply [2]. Thirdly, there is a venodilatory effect which reduces pre-load and may attenuate myocardial strain and oxygen demand [3].

However, these benefits have been brought into question after the landmark Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation trial (CRUSADE) observational study concluded that the use of morphine in Non-ST-Elevation Acute Coronary Syndrome (NSTE ACS) was associated with higher mortality [4]. Consequently, for NSTE ACS, the American Heart Association (AHA)/American College of Cardiology Foundation (ACCF) steering committee in 2014 have suggested the use of opioids at class IIb (Level of evidence: B) [5], while the European Society of Cardiology (ESC) guidelines in 2015 have only mentioned opioid use incidentally, noting its negative side effect profile (summarised in Table 3) [6]. While various other observational studies corroborate this negative effect on NSTE ACS, the clinical effects of opioids with STEMI patients remain unanswered.

Of greater clinical concern is that the beneficial effects of P2Y12 receptor antagonists in STEMI, may also be jeopardised by routine opioids administration, given their potential pharmacokinetic and pharmacodynamic interactions (Figure 1). Recent expert opinion has recommended cautious use of morphine in STEMI given its interactions with absorption of oral anti-platelets [7,8]. Despite the lack of robust evidence, both ESC and AHA/ACCF STEMI guidelines recommend opioid use [9,10].

This study aimed to synthesise evidence from randomised controlled trials (RCTs) and non-randomised, observational studies to investigate the effects of opioids in patients with STEMI.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) method was utilised for this review [11].

PICO Question

The Population, Intervention, Comparator, Outcome (PICO) question [12] was: ''In STEMI patients (P), does parenteral administration of opioids (I) compared with no administration of opioids (C) cause an increase in Major Adverse Cardiac Events (MACE) or a delay in anti-platelet activity (O)''. MACE is defined as a three-point composite evaluation of cardiovascular death, non-fatal myocardial infarction (MI) (including stent thrombosis) and non-fatal stroke; these outcomes will also be evaluated independently. Delay in anti-platelet activity will be evaluated based on patient's blood samples directly through proven laboratory assays analysing platelet reactivity and the plasma concentration of anti-platelets.

Inclusion Criteria and Study Selection

Randomised control trials and non-randomised, non-controlled observational studies which evaluated the role of parenteral opioid use as compared to no opioid use in patients with STEMI, as per the Joint ESC/ACCF/AHA/WHF task force for the third universal definition of myocardial infarction [13], were included. All published original research articles and conference abstracts, with no publication date or language restrictions, were evaluated. Animal studies, review articles, commentaries and expert editorials were excluded.

Information Sources

Studies from CENTRAL, EMBASE, Medline, Ovid Medline and PubMed up to 28 February 2018 were screened using the search strategy listed in the supplementary materials section.

Study Selection

One reviewer (JQSK) screened all abstracts to evaluate for eligibility based on the PICO question and inclusion criteria, with the full article reviewed in the event of ambiguity. In case of uncertainty despite analysis of the full article, eligibility was decided after discussion among all co-authors (JQSK, HF, DS). Additional papers not found through the search strategy, which were known by the authors prior, were added to the systematic review.

Data Extraction

All included studies had their data extracted using the recommendations from the Cochrane Handbook for Systematic Reviews [14]. In the case of missing information, the corresponding authors of the individual studies were contacted to access unpublished data. Categories on the data extraction sheet included: author(s), trial name, title, publication year, study design, MACE (in-hospital, 30-day, 1-year) and platelet reactivity.

Quality Assessment

The ''Cochrane Collaborations'' tool was utilised to evaluate for risk of bias at a study level [14]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was then applied to assess for bias at an outcome level [15].

Results

Study Selection and Evaluation

The initial search strategy (Supplementary Figure 1) yielded 121 studies. Two studies [16,17] were added from the reference list search of included studies. After duplicate studies were removed, 93 studies were reviewed and a further 74 were omitted.

Of the 19 studies, one was an RCT, and 18 were non-randomised, non-controlled observational studies, which included two conference abstracts [18,19] (Tables 1 and 2).

The only RCT was a single-centre, randomised, double-blind trial with patients assigned to receive intravenous morphine (5 mg) vs. placebo following a 180 mg loading dose

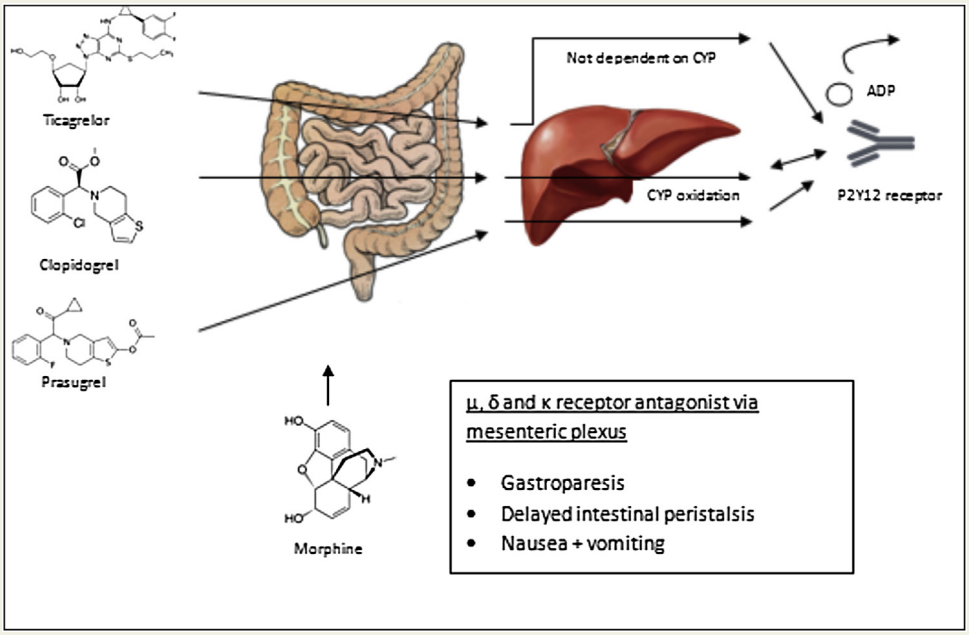

Figure 1 Opioid and P2Y12 inhibitor interactions.

of ticagrelor in patients with acute myocardial infarction; further analysis differentiated patients who had STEMI and NSTEMI [20]; this RCT investigated for platelet reactivity but not MACE.

Among the non-randomised, non-controlled observational studies, five evaluated for MACE only [16,19,21–23], 12 evaluated for platelet reactivity only [17,18,24–33] and one evaluated for both MACE and platelet reactivity [34]. The largest study that analysed MACE for STEMI patients with the administration of opioids utilised the FAST-MI 2005 (n = 1,726) and 2010 (n = 2,348) datasets [23]. The largest study to analyse the effect of opioids on platelet reactivity for STEMI patients was a post-hoc analysis of five other trials (n = 300) [30].

Assessment of Bias Within Studies

The risk of bias was assessed separately for RCTS and non-RCTs (Supplementary Table 1 and 2).

There was no significant form of bias in the RCT. However, the study was small (n = 74), and evaluated for both STEMI and NSTE ACS.

A large proportion of non-RCTs were biased by industry funding, eligibility criteria and confounding. Only four studies [16,22,25,27] clearly reported no industry funding, with the rest either being unclear or receiving industry funding. Eight (8) non-RCTs [17,18,26–29,31,32,34] did not evaluate the effect of opioids on STEMI outcomes; these studies involved a subgroup analysis of opioids on outcomes. All

Table 1 **RCTs evaluating opioid vs. placebo in STEMI patients for MACE and platelet reactivity.**

Study	Study design, aim of study and sample size	Decision regarding morphine	Length of F/U	MACE	Platelet reactivity
Kubica et al./ IMPRESSION, 2016. (20)	Single-centre, double-blinded RCT for AMI, n = 74	Randomised IV morphine (5 mg) vs. placebo	12hr post loading dose of ticagrelor 180 mg	Not studied	Pharmacokinetic Morphine use significantly associated with lower levels of circulating in first 12/24 (p = 0.004). Pharmacodynamic Morphine increased platelet reactivity when compared with placebo.

Legend: AUC: Area under plasma concentration time curve.

Abbreviations: RCT, srandomised control trials; STEMI, ST-Elevation myocardial infarction; MACE, major adverse cardiac events; AMI, acute myocardial infarction; IV, intravenous.

Table 2 Non-randomised, non-controlled/observational studies evaluating opioid vs. no opioids in STEMI patients for MACE and platelet reactivity.

Study	Study design, aim of study and sample size	P2Y12 inhibitor	MACE (opioid vs. no opioid)	Platelet reactivity (opioid vs no opioid)
Bellandi et al., 2016. [24]	Non-randomised, non-controlled for morphine in STEMI, n = 182	Ticagrelor 180 mg or prasugrel 60 mg	Not studied	Pharmacokinetic Morphine use significantly associated with delayed response to oral anti-platelet in first 8/24 (p = 0.001) post LD.
Bonin et al., 2018. [21]	Non-randomised, non-controlled for morphine on anterior STEMI 2 × 2 evaluation of cyclosporine and morphine, n = 969 (CIRCUS database)	Not specified	Morphine use not associated with significant difference in 1-year cardiovascular death (p = 0.88), recurrent MI (p = 0.08) or stroke (p = 0.82)	Not studied
Farag et al., 2018 [25]	Non-randomised, non-controlled for morphine for STEMI, n = 300	Clopidogrel 600 mg or ticagrelor 180 mg	Not studied	Pharmacodynamic Morphine use associated with significantly shorter OT (p < 0.001) and longer LT (p = 0.001) at baseline, and at 2/7 (p = 0.034) post LD.
Flierl et al., 2017 [34]	Non-randomised, non-controlled for morphine evaluating LD prasugrel for STEMI, n = 50	Prasugrel 60 mg	No significant difference for in-hospital or 30-day stent thrombosis, re-infarctions of cardiovascular deaths (n = 0)	Pharmacodynamic Morphine use associated with significantly delayed onset of platelet inhibition 1/24 post PCI (p < 0.01)
Franchi et al., 2015. [26]	Non-randomised, non-controlled for morphine evaluating escalating LD regimens of ticagrelor for STEMI patients undergoing PCI, n = 52	Ticagrelor (180 mg, 270 mg, 360 mg)	Not studied	Pharmacodynamic Morphine use associated with significantly higher PRU at 30/60 post LD (p = 0.018)
Iakobishvili et al./ACSIS, 2010 [16]	Non-randomised, non-controlled study for opioids for STEMI, n = 765	Not specified	PSA: 30-day mortality (non-discriminatory between cardiac vs. non-cardiac) significantly lower with IV opioids use (p = 0.04).	Not studied
Johnson et al., 2015 [27]	Non-randomised, non-controlled study for morphine for STEMI, n = 106	Prasugrel 60 mg	Not studied	Pharmacodynamic Morphine use associated with significantly higher levels of ADP at end of PCI (p < 0.001), 1/24 (p = 0.035) and 2/24 (p = 0.007) post.
McCarthy et al., 2017. [22]	Non-randomised, non-controlled study for STEMI, n = 1,287	Clopidogrel or ticagrelor (dose not specified)	Morphine use not associated with difference in in-hospital mortality (non-discriminatory between cardiac vs. non-cardiac) (p = 0.19)	Not studied
Parodi et al./ RAPID, 2013 [28]	Non-randomised, non-controlled study for morphine for STEMI, n = 50	Prasugrel 60 mg or ticagrelor 180 mg	Not studied	Pharmacodynamic Morphine use associated with significantly higher PRU at 2/24 post LD (p = 0.012)
Parodi et al./RAPID 2, 2014 [29]	Non-randomised, non-controlled study for morphine for STEMI, n = 50	Prausgrel 60 mg or ticagrelor 360 mg	Not studied	Pharmacodynamic Morphine use not significantly associated with higher PRU at all time periods post LD.

Table 2. (continued).

Study	Study design, aim of study and sample size	P2Y12 inhibitor	MACE (opioid vs. no opioid)	Platelet reactivity (opioid vs no opioid)
Parodi et al., 2015 [30]	Post hoc analysis of 5 non-randomised, non-controlled studies for morphine for STEMI, n = 300	Prasugrel 60 mg or ticagrelor (180 or 360 mg)	Not studied	Pharmacodynamic Morphine use associated with higher PRU at 2/24 ($p < 0.001$) post LD.
Puymirat E et al., 2016. [23]	Non-randomised, non-controlled study for morphine for STEMI from FAST-MI 2010, n = 2,348, and FAST-MI 2005, n = 1,726	Clopidogrel (dose not specified)	In hospital PSA: Morphine use not significantly associated with mortality (non-discriminatory between cardiac vs. non-cardiac) stent thrombosis or non-fatal recurrent MI. 1-year PSA: Morphine use not significantly associated with mortality (non-discriminatory between cardiac vs. non-cardiac). 1-year subgroup receiving thienopyridines in pre-hospital setting: Morphine use associated with decrease in mortality (non-discriminatory between cardiac vs. non-cardiac) ($p = 0.03$)	Not studied
Rollini et al./ CRUSH, 2016 [31]	Non-randomised, non-controlled study for morphine for STEMI patients, n = 50	Prasugrel 60 mg	Not studied	Pharmacodynamic Morphine use not associated with any significant changes to PRU at 2/24 post LD.
Siller-Matula et al., 2016. [32]	Non-randomised, non-controlled study for morphine for STEMI patients undergoing urgent PCI with abciximab vs. no abciximab bolus, n = 32	Prasugrel 60 mg	Not studied	Pharmacodynamic Morphine use associated with significant ADP induced platelet aggregation 3X higher median levels of ADP-induced aggregation at 2/24 among the non-abciximab group ($p = 0.019$) post LD.
Silvain et al./ PRIVATE-ATLANTIC, 2016 [33]	Non-randomised, non-controlled study for morphine for STEMI patients receiving LD of ticagrelor pre-hospital vs in-hospital, n = 37	Ticagrelor 180 mg	Not studied	Pharmacodynamic Morphine use associated with significantly delayed onset of platelet inhibition post PCI at 1/24 ($p = 0.0116$) and 6/24 ($p = 0.0057$)
Venetsanos et al., 2017 [18]	Non-randomised, non-controlled study for morphine for STEMI before PCI for bivalirudin vs. heparin, n = 103	Not specified	Not studied	Pharmacodynamic Morphine use associated independent predictors of HRPR at 1/24 post LD.

Table 2. (continued).

Study	Study design, aim of study and sample size	P2Y12 inhibitor	MACE (opioid vs. no opioid)	Platelet reactivity (opioid vs no opioid)
Vercellino et al., 2016 [19]	Non-randomised, non-controlled study for opioid for STEMI, n = 533	Not specified	Morphine use not associated with increased in-hospital mortality (non-discriminatory between cardiac vs. non-cardiac) or in-hospital MACE. PSA at median follow-up of 1,038 days, all-cause mortality not increased with morphine use (HR = 1.142 (0.606–2.153))	Not studied
Xanthopoulou et al. 2015 [17]	Non-randomised, non-controlled pooled multivariate analysis for factors affecting platelet reactivity 2/24 post P2Y12 receptor antagonist LD STEMI, n = 207	Clopidogrel 600 mg, ticagrelor 180 mg or prasugrel 60 mg	Not studied	Pharmacodynamic Morphine use associated with higher platelet reactivity at 2/24 post LD ($p < 0.001$).

Abbreviations: ADP; adenosine diphosphate levels, HR, hazard ratio; HRPR, high residual platelet reactivity; LD, loading dose; LT, lysis time; OR, odds ratio; OT, occlusive time; p, p-value; PCI, percutaneous coronary intervention; PSA, propensity score analysis; PRU, P2Y12 reaction units; VASP, vasodilator-associated stimulated phosphoprotein; STEMI, ST-Elevation myocardial infarction; MACE, major adverse cardiac events; AMI, acute myocardial infarction.

Outcomes

The findings are summarised in Tables 1 and 2. Due to the heterogeneity of studies and outcomes measured, there was no pooling of outcomes.

MACE

While in-hospital events were documented in the RCT [20], they were not specific to STEMI patients, and were neither

Table 3 Guideline recommendations regarding morphine use in STEMI and UA/NSTEMI.

Guideline	Year	Recommendation of morphine in STEMI	Class	Level of evidence	Year	Recommendation of morphine in UA/NSTEMI	Class	Level of evidence
ESC	2017 (9)	Titrated IV opioids considered to relieve pain	IIa	C	2015 (6)	Morphine reserved for persisting severe chest pain with caveat of slowing intestinal absorption of oral platelet inhibitors	–	–
ACCF/ AHA	2013 (10)	Morphine drug of choice for pain relieve especially if complicated by APO	–	–	2014 (5)	In absence of C/I: reasonable to administer IV morphine if persistent chest pain despite treatment with maximally tolerated anti-ischaemic therapy	IIb	B

Abbreviations: ESC, European Society of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; STEMI, ST-Elevation myocardial infarction; IV, intravenous; UA, unstable angina; APO, acute pulmonary oedema.

the primary nor secondary endpoints. Hence, MACE cannot be evaluated.

Major adverse cardiac events were evaluated in the minority (n = 6) of non-randomised, non-controlled observational studies. Among these six studies, clinical outcomes were evaluated in-hospital, at 30 days, at 1 year and in one study at 3 years. However, the clinical endpoints were heterogenous, with no standardised definition of MACE. Although four studies [19,21,22,34] showed no significant difference in outcomes, these studies either evaluated MACE individually or included other clinical outcomes beyond the paper's definition of MACE (e.g. unstable angina, re-admission or all-cause mortality). Two (2) studies showed significant difference, with Iakobishvili et al. reporting a reduction in mortality at 30 days [16] and Puymirat et al. reporting a reduction at 1 year in a subgroup analysis [23] associated with morphine use. However, these were secondary endpoints, involved sub-group analysis and did not discriminate between cardiac and non-cardiac cause of mortality.

Platelet Reactivity

In Kubica et al. [20], the primary endpoints of platelet reactivity were not distinguished between STEMI and NSTE ACS; although this study demonstrated that parenteral morphine administration was associated with increased platelet reactivity levels overall, there was no specific data for STEMI patients. Pharmacokinetically, the study demonstrated a decrease in ticagrelor plasma concentration after adjustment for acute myocardial infarction (AMI) type (p = 0.004).

Seventeen (17) non-randomised, non-controlled observational studies evaluated platelet reactivity. However, there was significant heterogeneity in assays used, measurement timings and type of P2Y12 receptor inhibitors. Studies that evaluated platelet reactivity 1-hour post administration of loading dose of P2Y12 inhibitors corroborate a significant increase in platelet reactivity with opioid administration. Platelet reactivity at 2 hours from loading dose is equivocal. Farag et al. [25] concluded that this effect persists till day 2 post opioid and P2Y12 inhibitor loading dose administration. Three (3) studies [27,33,34] that evaluated platelet reactivity timing based on the timing of primary percutaneous coronary intervention (PPCI), instead, also corroborated an increase in platelet reactivity.

Discussion

This systematic review highlights that opioid administration is significantly associated with increased platelet reactivity in STEMI patients. The effects of opioid administration on major clinical outcomes remain equivocal and largely unknown. Most importantly, this review highlights the paucity of quality research evaluating the effect of opioid on STEMI patients, especially within the context of modern STEMI systems of care.

The role of opioid administration on platelet reactivity has been investigated extensively. Hobl et al. studied the effect of morphine on healthy volunteers using clopidogrel (n = 24) [35], ticagrelor (n = 24) [36] and prasugrel (n = 12) [37] with a robust study design (randomised, controlled, crossover). These studies demonstrated a significant decrease in maximal plasma concentration of all P2Y12 inhibitors, confirming that opioids impair the pharmacokinetics of P2Y12 inhibitors. However, regarding pharmacodynamics, the results are mixed; clopidogrel was associated with significantly higher platelet reactivity levels with concomitant morphine administration, whereas ticagrelor and prasugrel had no significant difference in platelet reactivity levels. While these studies confirm the gastroparetic effect of opioids [38], the disparity between the pharmacodynamic effect of STEMI patients observed in this systematic review with the ticagrelor and prasugrel studies may be explained by a number of reasons. Firstly, STEMI patients may have impaired gastrointestinal resorption secondary to reduced splanchnic circulation [39] and this may, consequently, delay its effect as compared to healthy patients. This different physiological state is confirmed by two other studies, which demonstrates impaired pharmacodynamic effects for prasugrel (in patients with prior STEMI [38]) and ticagrelor (in elective percutaneous coronary intervention [40]). Secondly, opioid's potential interactions with other important treatments, especially aspirin, have not been included in the studies with healthy volunteers [41]; the pharmacokinetic and pharmacodynamic inhibitory effect of opioids on aspirin could further increase platelet reactivity. Thirdly, the studies in the systematic review did not discriminate between the types of P2Y12 inhibitors utilised, and the results may be less reflective of particular P2Y12 inhibitors. Several review articles that have evaluated opioid administration and P2Y12 receptor antagonists [42–44] have included healthy volunteers and patients with NSTE ACS, which potentially confounds the effect of opioids on platelet reactivity in STEMI patients. Fourthly, given the increased potency of ticagrelor and prasugrel, lower drug plasma concentrations may still achieve adequate antiplatelet effects. Lastly, platelet function testing at different time points in different studies post morphine and antiplatelet administration is likely to lead to differing results.

As evidenced by this review, there is no demonstrable significant difference with opioid administration on clinical outcomes in STEMI patients. In fact, two studies suggest a possible benefit with opioid administration [16,23]; in its propensity matched analysis, Iakobishvili et al. reported a significantly lower all-cause 30-day mortality associated with parenteral opioid use (2.4% vs. 6.2%, p = 0.04), while Puymirat et al. had a subgroup analysis of patients receiving prehospital thienopyridines having a significant decrease in all-cause 1-year mortality with opioid administration (2.4% vs. 5.9%, HR = 0.45, 95% CI 0.21–0.93, p = 0.03). However, the authors report a selection bias, where patients receiving parenteral opioids were younger, more likely to undergo reperfusion and had a lower GRACE risk score.

This is in contrast to NSTE ACS, where observational studies have highlighted a significant increase in mortality with the use of opioids [4,22]. This could be hypothesised by

the effect of emergent PPCI in STEMI outweighing the pharmacodynamic effect of opioids on P2Y12 inhibitors; as compared to NSTE ACS, delayed PPCI may prolong the impaired pharmacodynamic of P2Y12 inhibitors and increase the frequency of coronary thrombus [22].

Some studies have reported different methods of measuring the effect of opioids on STEMI. De Waha et al. [45] measured the effect of opioids on STEMI patients using cardiac magnetic resonance imaging (CMR) within a median of 3 days post index event and reported a larger infarct size, higher extent of microvascular obstruction (MO), and lower myocardial salvage index (MSI) in the intravenous (IV) morphine group vs. non-IV morphine group ($p < 0.05$). Intravenous morphine was also identified as an independent predictor for suboptimal reperfusion success. However, this was not associated with a significant difference in clinical outcomes. Conversely, Gwag et al. [46] investigated intracoronary administration of morphine but failed to demonstrate a significant difference in infarct size, MO and MSI. These mixed results suggest the pleiomorphic effect of opioids. Leurent et al. [47] studied the effects of prehospital IV morphine on infarct-related artery patency in STEMI patients but did not find any significant difference, with a non-significant trend towards stent thrombosis ($p = 0.09$) in patients administered IV morphine.

Morphine is the predominant opioid analgesic of choice in the studies, as evidenced by this systematic review. While other opioid receptor agonists, like fentanyl [48] and alfentanil [49], have been studied for undifferentiated pre-hospital ischaemic-like chest pain, their role in confirmed STEMI on the pharmacokinetic and pharmacodynamic effect on P2Y12 inhibitors and clinical outcomes have not been as thoroughly investigated; whether opioids affect STEMI as a class effect needs further clairifcation.

Given the need for adequate pain relief in STEMI often beginning in the pre-hospital environment, there would be a number of challenges to performing a randomised controlled trial. Such a study would require randomisation by Emergency Service Personnel and require study of alternative analgesic agents. The ideal analgesic should have little gastroparetic effect, thereby not impacting platelet reactivity of P2Y12 inhibitors. Possible agents could include intravenous acetaminophen [50], synthetic opioids like alfentanil or intravenous sodium channel inhibitors like lidocaine [51]. Similar to the recent RCTs questioning the role of oxygen in STEMI including the Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction (AVOID) [52] and DETermination of the role of Oxygen in suspected Acute Myocardial Infarction (DETO2X) [53] trials for oxygen use in STEMI, there is a pressing need to RCTs investigating the impact of opioids in STEMI patients.

Limitations

Despite an extensive search strategy, the non-randomised, non-controlled studies (17/18) limited the impact of analysis due to their potential confounding bias. Furthermore, due to the heterogenous data (P2Y12 inhibitor, platelet reactivity, clinical outcomes (and lack thereof)), a meta-analysis could not be performed.

Conclusion

This systematic review highlights the paucity of randomised controlled trials evaluating the effect of opioid administration on outcomes in STEMI patients. Current literature corroborates that opioid administration is associated with prolonged platelet reactivity in the emergent timeframe. However, whether this affects clinical outcomes is unknown. There is a need for adequately powered RCTs to investigate the impact of opioids on clinical and pharmacological endpoints.

Conflict of Interest

No conflict of interest to declare.

Dr Dion Stub's research is supported by a National Heart Foundation Fellowship and Viertel Foundation Grant. Dr Karlheinz Peter is funded by a Principal research fellowship of the National Health and Research Council of Australia.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.hlc.2018.12.015.

References

[1] Mackenzie J. Angina Pectoris. Oxford Medical Publication; 1923.
[2] Herlitz J, Hjalmarson A, Waagstein F. Treatment of pain in acute myocardial infarction. Br Heart J 1989;61(1):9–13.
[3] Zelis R, Mansour EJ, Capone RJ, Mason DT. The cardiovascular effects of morphine. The peripheral capacitance and resistance vessels in human subjects. J Clin Invest 1974;54(6):1247–58.
[4] Meine TJ, oe MT, Chen AY, Patel MR, Washam JB, Ohman EM, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE quality improvement initiative. Am Heart J 2005;149(6):1043–9.
[5] Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes Jr D, et al. AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes. Circulation 2014;130:e344–426.
[6] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2015;37:267–315.
[7] Dan Atar, Stefan A. Morphine in myocardial infarction: balancing on the tight rope. Eur Heart J 2016;37:253–5.
[8] Parodi G. Editor's choice-chest pain relief in patients with acute myocardial infarction. Eur Heart J 2016;5(3):277–81.
[9] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. ESC guidelines for themanagement of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2017;(39):119–77.

[10] O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al. ACCF/AHA guideline for the management of ST-elevation myocardial infarction. JACC 2013;61(4):e78–140.
[11] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9.
[12] Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. ACP J Club 1995;123 (3):A12–3.
[13] Thygesen K, Alpert JS, affe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. Circulation 2012;126 (16):2020–35.
[14] Higgins J, Green S. Cochrane handbook for systematic reviews of intervention. Chichester, West Sussex/Hoboken NJ: John Wiley & Sons; 2008.
[15] Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is ''quality of evidence" and why is it important to clinicians? BMJ 2008;336(7651):995–8.
[16] Iakobishvili Z, Porter A, Battler A, Behar S, Roth A, Atar S, et al. Effect of narcotic treatment on outcomes of acute coronary syndromes. Am J Cardiol 2010;105(7).
[17] Xanthopoulou I, Davlouros P, Tsigkas G, Koutsogiannis N, Patsilinakos S, Deftereos S, et al. Factors affecting platelet reactivity 2 hours after P2Y12 receptor antagonist loading in primary percutaneous coronary intervention for ST-elevation myocardial infarction. Circ J 2015;80(2):442–9.
[18] Venetsanos D, Swahn E, Lawesson SS, Gustafsson KM, Erlinge D, Lindahl TL, et al. Platelet activity in primary percutaneous coronary intervention patients randomized to bivalirudin or heparin. In: Resuscitation Science Symposium; United States: Circulation; 2017.
[19] Vercellino M, Sanchez FA, Boasi V, Tacchi C, Perri D, Pansecco E, et al. Observational monocentric registry ''CARDIO-STEMI SANREMO": effects of morphine administration in STEMI patients and its association with clinical in-hospital outcomes and long-term mortality. Eur Heart J 2016;178–9.
[20] Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J 2016;37:245–52.
[21] Bonin M, Mewton N, Roubille F, Morel O, Cayla G, Angoulvant D, et al. Effect and safety of morphine use in acute anterior ST-segment elevation myocardial infarction. J Am Heart Assoc 2018;7(4).
[22] McCarthy CP, Bhambhani V, Pomerantsev E, Wasfy JH. In-hospital outcomes in invasively managed acute myocardial infarction patients who receive morphine. J Interventional Cardiol 2017.
[23] Puymirat E, Lamhaut L, Bonnet N, Aissaoui N, Henry P, Cayla G, et al. 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 Acute ST-elevation and non-ST-elevation Myocardial Infarction) programme. Eur Heart J 2016;37(13):1063–71.
[24] Bellandi B, Zocchi C, Xanthopoulou I, Scudiero F, Valenti R, Migliorini A, et al. Morphine use and myocardial reperfusion in patients with acute myocardial infarction treated with primary PCI. Int J Cardiol 2016;221:567–71.
[25] Farag M, Spinthakis N, Srinivasan M, Sullivan K, Wellsted D, Gorog DA. Morphine analgesia Pre-PPCI Is Associated with prothrombotic state, reduced spontaneous reperfusion and greater infarct size. Thrombosis Haemostasis 2018;118(3):601–12.
[26] Franchi F, Rollini F, Cho JR, Bhatti M, DeGroat C, Ferrante E, et al. Impact of escalating loading dose regimens of ticagrelor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of a prospective randomized pharmacokinetic and pharmacodynamic investigation. JACC Cardiovasc Interv 2015;8(11):1457–67.
[27] Johnson TW, Mumford AD, Scott LJ, Mundell S, Butler M, Strange JW, et al. A Study of platelet inhibition, using a 'Point of Care' platelet function test, following primary percutaneous coronary intervention for ST-elevation myocardial infarction [PINPOINT-PPCI]. PLoS One 2015;10(12):e0144984.
[28] Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity Of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013;61(15):1601–6.
[29] Parodi G, Bellandi B, Valenti R, Migliorini A, Marcucci R, Carrabba N, et al. Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial infarction patients: the Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary PCI 2 study. Am Heart J 2014;167(6):909–14.
[30] Parodi G, Bellandi B, Xanthopoulou I, Capranzano P, Capodanno D, Valenti R, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. Circ Cardiovasc Interv 2015;8(1):e001593.
[31] Rollini F, Fanchi F, Hu J, Kureti M, Aggarwal N, Durairaj A, et al. Crushed prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary intervention: the CRUSH study. J Am Coll Cardiol 2016;67(17):1994–2004.
[32] Siller-Matula J, Specht S, Kubica J, Alexopoulos D, De Caterina R, Hobl EL. Abciximab as a bridging strategy to overcome morphine-prasugrel interaction in STEMI patients. Br J Clin Pharmacol 2016;82 (1):1343–50.
[33] Silvain J, Storey RF, Cayla G, Esteve JB, Dillinger JG, Rousseau H, et al. P2Y12 receptor inhibition and effect of morphine in patients undergoing primary PCI for ST-segment elevation myocardial infarction. The PRIVATE-ATLANTIC study. Thrombosis Haemostasis 2016;116(2):369–78.
[34] Flierl U, Zauner F, Jan Sleweke, Berliner C, Nappo LC, Tillmanns J, et al. Efficacy of prasugrel administration immediately after percutaneous coronary intervention in ST-elevation myocardial infarction. Thrombosis Haemostasis 2017;117(1):99–104.
[35] Hobl EL, Stimpfl T, Ebner J, Schoergenhofer C, Derhaschnig U, Sunder-Plassmann R, et al. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol 2014;63(7):630–5.
[36] Hobl EL, Reither B, Schoergenhofer C, Schwamesis M, Derhaschnig U, Kubica J, et al. Morphine decreases ticagrelor concentrations but not its antiplatelet effects: a randomized trial in healthy volunteers. Eur J Clin Invest 2016;46(1):7–14.
[37] Hobl EL, Reiter B, Schoergenhofer C, Schwamesis M, Derhaschnig U, Lang IM, et al. Morphine interaction with prasugrel: a double-blind, cross-over trial in healthy volunteers. Clin Res Cardiol 2016;105 (4):349–55.
[38] Nimmo WS, Heading RC, Wilson J, Tothill P, Prescott LF. Inhibition of gastric emptying and drug absorption by narcotic analgesics. Br J Clin Pharmacol 1975;2(6):509–13.
[39] Bochner F, Lloyd L. Aspirin for myocardial infarction. Clinical pharmacokinetic considerations. Clin Pharmacokinet 1995;28(6):433–8.
[40] McEvoy JW, Ibrahim K, Kickler TS, Clarke WA, Hasan RK, Czarny MJ, et al. Effect of intravenous fentanyl on ticagrelor absorption and platelet inhibition among patients undergoing percutaneous coronary intervention: the PACIFY randomized clinical trial (platelet aggregation with ticagrelor Inhibition and fentanyl). Circulation 2018;137(3):307–9.
[41] Hobl EL, Schmid RW, Stimpfl T, Ebner J, Jilma B. Absorption kinetics of low-dose chewable aspirin - implications for acute coronary syndromes. Eur J Clin Invest 2015;45(1):13–7.
[42] Abdikarim Abdi, Bilgen B. An evidence-based review of pain management in acute myocardial infarction. J Cardiol Clin Res 2016;4(4):1067.
[43] Giannopoulos G, Deftereos S, Kolokathis F, Xanthopoulou I, Lekakis J, Alexopoulos D. P2Y12 receptor antagonists and morphine: a dangerous liaison? Circ Cardiovasc Interv 2016;9(9):e004229.
[44] Kubica J, Kubica A, Jilma B, Adamski P, Hobl EL, Navarese EP, et al. Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors. Int J Cardiol 2016;215:201–8.
[45] de Waha S, Eitel I, Desch S, Fuernau G, Lurz P, Urban D. Intravenous morphine administration and reperfusion success in ST-elevation myocardial infarction: insights from cardiac magnetic resonance imaging. Clin Res Cardiol 2015;104(9):727–34.
[46] Gwag HB, Kim EK, Park TK, Lee JM, Yang JH, Song YB, et al. Cardioprotective effects of intracoronary morphine in ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: a prospective, randomized trial. J Am Heart Assoc 2017;6(4).
[47] Leurent G, Coudert I, Auffret V, Bot E, Le Breton H. Is prehospital intravenous morphine administration associated with a lower infarct-related artery patency? Insight from a ST-segment elevation myocardial infarction prospective registry. Eur Heart J 2016;37(Abstract Supplement):177.
[48] Weldon ER, Ariano RE, Grierson RA. Comparison of fentanyl and morphine in the prehospital treatment of ischemic type chest pain. Prehosp Emerg Care 2016;20(1):45–51.
[49] Silfvast T, Saarnivaara L. Comparison of alfentanil and morphine in the prehospital treatment of patients with acute ischaemic-type chest pain. Eur J Emerg Med 2001;8(4):275–8.

[50] Sin B, Wai M, Tatunchak T, Motov SM. The use of intravenous acetaminophen for acute pain in the emergency department. Acad Emerg Med 2016;23:543–53.
[51] Fitzpatrick Brendan Michael, Mullins ME. Intravenous lidocaine for the treatment of acute pain in the emergency department. Clin Exp Emerg Med 2016;3(2):105–8.
[52] Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation 2015;131(24):2143–50.
[53] Hofmann R, James SK, Svensson L, Witt N, Frick M, Lindahl B, et al. DETermination of the role of OXygen in suspected acute myocardial infarction trial. Am Heart J 2014;167(3):322–8.