Morphine Use in ST-Elevation Myocardial Infarction With Downstream P<sub>2</sub>Y<sub>12</sub> Receptor Blockers—Insight From Observational Study

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Abstract

**Background and Aims:** Morphine use for patients presenting with NSTE-ACS is associated with excess mortality. However, the role of morphine in STE-ACS is ill characterized. We have recently confirmed direct prothrombotic effect of morphine using murine models. We sought to explore whether morphine use in STE-ACS patients, used to be scheduled for downstream P<sub>2</sub>Y<sub>12</sub> blockers, is negatively associated with procedural and clinical outcomes. **Methods:** A single-center, observational retrospective analysis enrolling 130 non-randomized stable patients sustaining STE-ACS as their first manifestation of coronary disease, who presented between December 2010 and June 2013. All were managed by early invasive approach. Of study patients, 55 were treated by morphine, and 75 were not. All were administered downstream P<sub>2</sub>Y<sub>12</sub> blockers according to an already abandoned local policy. Outcomes evaluated included TIMI grade flow, thrombus burden, ST-segment resolution, myocardial function by echocardiography, and cardiovascular death. **Results:** Morphine administration was associated with a significantly higher incidence of impaired final TIMI grade flow (TIMI < 3, 40% vs 4%, \(P < .05\)), lower incidence of ST-segment resolution >70% (40.7% vs 76.5%, \(P < .05\)), and a higher incidence of moderate or severe systolic dysfunction (48.1% vs 29.1%, \(P < .05\)) compared with morphine naive patients. Interestingly, the overall mortality rate was higher in the morphine-treated group (18% vs 5.3%, \(P < .05\)). **Conclusions and Relevance:** Morphine administration combined with the downstream P<sub>2</sub>Y<sub>12</sub> blockers practice signify a group with a higher occurrence of impaired myocardial reperfusion and cardiovascular death despite established on-time primary angioplasty.

Keywords

morphine, no-reflow, thrombosis, downstream

Introduction

STE-ACS remains one of the leading life-threatening conditions encountered in clinical practice. Primary percutaneous coronary intervention (PPCI) is largely considered the treatment of choice for coronary mechanical reperfusion. Parallel to PPCI, the potent opioid morphine has claimed a fundamental role as the ultimate analgesic for ischemic pain. The most persuasive argument for morphine uses in STE-ACS patients in pain and duress is its cogent anxiolytic effect which may halt sympathetic activation and its associated deleterious effects. In addition, morphine has inherent hemodynamic effects that are potentially beneficial during myocardial ischemia. By depressing the sympathetic tone, morphine lowers both cardiac preload and afterload, thus reducing myocardial oxygen demand. Nevertheless, the safety and efficacy of morphine in the setup of STE-ACS were not substantiated by prospective blinded randomized outcome trials. Still, the American Heart Association/American College of Cardiology guidelines recommend the use of morphine for pain control in the presence of myocardial ischemia (class IC indication). Recently, several
studies have raised significant doubts regarding the safety of routine morphine administration, the benchmark being the CRUSADE registry. The observational CRUSADE study showed that morphine therapy in NSTEMI patients was associated with increased mortality. This analysis led to the relegation of morphine status by the AHA guidelines from class IC to IIB in patients presenting with NSTEMI. In addition, morphine was criticized for inhibiting and delaying the absorption and thus the effect of P2Y12 inhibitors, diminishing their net therapeutic effect. Moreover, we have recently confirmed a direct prothrombotic effect of morphine using validated murine thrombosis models. Morphine aggravated platelet adhesion and significantly shortened the primary clot formation time in Thromboelastography. Although these facts and the observation of increased mortality in the CRUSADE registry raise concerns regarding possible deleterious effect of morphine in STE-ACS patients, the net effect of morphine in this setting has yet to be elucidated. Therefore, we sought to evaluate for conceivable association between morphine use and both epicardial coronary flow and myocardial perfusion in STE-ACS patients.

Methods

Study Group

We retrospectively screened all consecutive STE-ACS patients, without previous IHD, treated at our institution between December 2010 and June 2013. During this period, having no on-site surgical backup, most of our patients were administered P2Y12 inhibitors at the end of the intervention, practically providing protracted sub-therapeutic antiplatelet window. We thought that this vulnerable period might help delineating possible pro/anti-thrombotic effects of morphine. Hemodynamically unstable patients on arrival, upstream DAPT loaded patients, late arrival patients (presented to the hospital more than 6 hours following chest pain onset), and those with prior myocardial infarction, previous PCI or CABG were excluded. Eligible patients were divided into 2 groups based on pre-treatment with intravenous morphine before PCI. The primary endpoints assessed were gross reperfusion indices: ST-segment resolution on the ECG at 90 min post PCI, TIMI flow grade and thrombus burden scale throughout the procedure, as well as systolic cardiac function on echocardiography. Secondary endpoints included tirofiban and/or adenosine administration, application of aspiration thrombectomy and the need for intra-aortic balloon pump (IABP) support. Short- and long-term mortality was verified according to data from the Ministry of the Interior. Mortality was ascertained through January 2017.

Electrocardiographic Analysis

Electrocardiograms were obtained at admission and at 90 min after the completion of PCI. Two physicians blinded to the angiographic and clinical findings independently performed ST-segment measurements. ST-segment deviation was measured at the J point with the line connecting the preceding and following PR segment as the reference baseline. The scoring was dichotomous: 1 for ST resolution >70% from baseline, and 0, if not.

Qualitative Angiographic Analysis

Coronary angiograms were analyzed by 2 experienced interventional cardiologists blinded to patients’ allocation, who provided the following scores:

1. TIMI flow grade score (0-3) before PCI, after wire crossing, after balloon inflation and finally after stent implantation.
2. Thrombus burden score (0-5) before PCI and after wire passage was determined according to the following: 0, no thrombus; 1, possible thrombus; 2, small [greatest dimension ≤0.5 vessel diameter (VD)]; 3, moderate (>0.5 but <2VD); 4, large (≥2VD); 5, total vessel occlusion.

Echocardiographic Data

Transthoracic echocardiography was reported in the standard manner during hospitalization, with left ventricular ejection fraction (LVEF) calculated using the biplane Simpson’s method. Based on the American Society of Echocardiography Classification LVEF was categorized as normal (≥55%), mildly (45%-54%), moderately (30%-44%) or severely reduced (<30%).

Statistical Analysis

Continuous variables are presented as a mean and standard deviation, and categorical data are presented as percentages. Categorical variables were compared using Pearson chi square test, while continuous variables were compared using the student’s t test or the Mann U Whitney test, as appropriate. All statistical analyses were performed on IBM SPSS version 26. Statistical significance was set at the 2-tailed 0.05 level, without multiplicity adjustment.

Results

Two-hundred and seventy-nine patients were screened between December 2010 and June 2013. Figure 1 displays the flow diagram used for patients’ selection. Out of them, 130 individuals met the eligibility criteria and were included in the study (149 were excluded; 101, upstream DAPT loading; 17, hemodynamically unstable; 20, with previous heart disease; and 11, late arrival). One hundred nineteen patients (67%) were brought in by an ambulance while the rest were self-referred. Morphine administration was at the physician’s/paramedic’s discretion. Overall, 55 patients (42.3%) were treated with peri-procedural morphine, while 75 were morphine naive. There was no significant difference in the distribution of the infarct related artery between the groups. In the morphine-naive group the infarct related artery was most frequently the left anterior
descending (LAD, in 33 patients, 44%) followed by the right coronary artery (RCA, in 31 patients, 41%), and the left circumflex coronary artery (LCX, in 11 patients, 15%). Among the morphine-treated group, 26 patients were with LAD (47%), 21 due to RCA (38%) and 8 patients with LCX (15%) involvement ($P = \text{NS}$).

Table 1 shows the baseline characteristics of study population, according to morphine use. Overall, both groups were comparable regarding the presence of risk factors for coronary artery disease, including chronic renal failure (an estimated glomerular filtration rate <60 ml/min/1.73 m², persisting for ≥3 months) which was insignificantly higher in the morphine group. There were no statistically significant differences in relation to pain onset to reperfusion time interval, Killip class at presentation or other pre-interventional pharmacological treatments between groups.

We observed substantial differences among study groups regarding the angiographic findings (Table 2). The morphine group presented significantly higher thrombus burden before wire crossing. Furthermore, the epicardial flow at the different stages of the procedure, as observed from pre-intervention through wire passage, after balloon inflation and up to stent deployment, was more disturbed with morphine (Figure 2). The former indices were associated with a higher use of aspiration thrombectomy (40.4% vs 9.6%, $P < .001$). Moreover, pharmacological management including tirofiban and adenosine administration, in addition to IABP support, were more utilized in the morphine group (Table 2). Notably, the compromised epicardial flow was in concordance with significantly higher incidence of poor ST-segment resolution (40.7% vs 76.5%, $P < .05$), and higher occurrence of impaired left ventricular systolic function in the morphine group (48.1% vs 29.1% with moderate to severe systolic dysfunction).

Morphine use was also associated with negative mortality outcomes. The mortality rate with morphine was 18% (50% in hospital, 70% within 3 months, 90% with moderate-severe LV dysfunction, mean age 61.1 years) and 5.3% among morphine naive patients (25% in hospital, 50% within 3 months, 100% with moderate-severe LV dysfunction, mean age 69 years), $P < .05$.

**Discussion**

$P_{2Y12}$ inhibitors loading at the first medical contact is mandatory as advocated by practice guidelines, followed by primary mechanical reperfusion. Nonetheless, reasonable considerations exist for downstream administration of the $P_{2Y12}$ blockers until the coronary anatomy is defined, essentially the anticipation of potential need for emergent CABG in some patients, where the avoidance of platelet inhibition would negate bleeding risk. Recent studies resulted in concerns regarding the safety of morphine administration during acute coronary events as there were no randomized trials testing routine morphine use for STE-ACS patients, and probably these will not be performed. Here we describe worse angiographic and clinical outcomes associated with morphine use in a specific setup of downstream $P_{2Y12}$ blockers administration.

A recently published review and meta-analysis inferred that morphine administration was not associated with adverse in-hospital or 30-day clinical events in patients undergoing primary PCI for STE-ACS. To the best of our knowledge, the negative association between morphine use and the occurrence of poor ST-segment resolution, impaired left ventricular systolic function and increased mortality has not been described before. Overall, this association is either morphine related, or a chance finding as morphine was administrated to a sicker group; in our study, hemodynamically unstable patients were excluded, and the baseline clinical characteristics were similar in both arms.
Unlike previous groups addressing morphine use in STE-ACS in which the default was upstream P2Y12 inhibitors loading, in the current study the administration was unanimously post stenting. We have shown that throughout all the stages of the intervention the morphine requiring group demonstrated inferior epicardial flow with a decompensated outcome compared to the morphine naive group: the TIMI grade flow was lower at the pre-intervention stage known to forecast unfavorable outcomes, after wiring of the culprit artery, a well-established risk marker for increased mortality, after balloon inflation, and finally following stent implantation. Similarly, the pre-intervention thrombus burden and that after wiring were higher in the morphine group. Moreover, and although at the discretion of the operator, the utilization of IABP, aspiration thrombectomy, and the administration of pharmacological agents to improve flow were significantly higher in the morphine group.

Farag et al showed that morphine administered in the pre-hospital setting was linked to enhanced platelet reactivity and impaired endogenous fibrinolysis, with a concomitantly reduced rate of spontaneous ST-segment resolution, and reduced TIMI grade flow at presentation. Despite these negative parameters at presentation, this was eventually neither translated to compromised TIMI grade flow post recanalization nor to reduced myocardial function. Administration of glycoprotein IIb/IIIa inhibitors was proved to negate the adverse effects of morphine.

All patients in the study by Farag et al were loaded with dual antiplatelet therapy (DAPT), including ticagrelor, 46 min before angiography, while our default P2Y12 inhibitor was clopidogrel, with established platelet inhibitory effect of only 20% after 2 hours. Furthermore, the door to first device time was shorter in the study by Farag et al, 29-30 versus 74 min. Intriguingly, although our local pharmacological setup and the relative time delay from pain to needle were similar regardless of morphine use, the morphine-naive group was marginally affected, if at all. It seems that the combination of early DAPT loading (better ST-resolution following PCI in the ATLANTIC study and French Registry 2010), high rate of upstream tirofiban (better reperfusion 1-hour post PCI as in the ON-TIME 2 study), the short pain-to-door, and the door-to-balloon time intervals, all contributed to early therapeutic platelet inhibition and better outcomes in the morphine arm in the study by Farag et al compared to our morphine group. Consistent with the results by Farag et al, a sub-group analysis of the ATLANTIC study showed no morphine use to be associated with a substantial improvement in spontaneous ST resolution.

Furthermore, morphines induced emesis can reduce intestinal motility, thereby delaying the absorption of orally administered P2Y12 inhibitors. To reconcile the ambiguity regarding morphines effect on P2Y12 inhibitors we summarized the available data in the literature concerning the pharmacodynamics of P2Y12 at different time points, with or without

### Table 2. Coronary Angiography Variables With and Without Morphine.

| Variable                          | Morphine group | No morphine group | P value |
|-----------------------------------|----------------|-------------------|---------|
| Pain duration (hours)             | 3.4            | 3                 | .5      |
| TIMI thrombus scale (before intervention) | 4.42          | 3.27              | <.01    |
| TIMI thrombus scale (post wire)   | 2.68           | 2.11              | .07     |
| TIMI flow at presentation         | 0.54 (69.1%)   | 1.1 (50.7%)       | .02     |
| TIMI flow post wire               | 0.87 (47.3%)   | 2.03 (9.34%)      | <.001   |
| TIMI flow post balloon            | 1.64           | 2.68              | <.001   |
| TIMI flow post stent              | 2.38           | 2.96              | <.001   |
| TIMI flow <3 post stent           | 40.4%          | 4.1%              | <.001   |
| Adenosine administration          | 12.8%          | 10.1%             | .42     |
| Tirofiban administration          | 34%            | 20.5%             | .09     |
| Thrombus aspiration               | 40.4%          | 9.6%              | <.001   |
| IABP                              | 17.6%          | 0%                | .01     |
| Poor ST segment resolution        | 76.5%          | 40.7%             | <.05    |
| Moderate-severe LV dysfunction    | 48.1%          | 29.1%             | <.05    |

Abbreviations: TIMI, thrombolysis in myocardial infarction; IABP, intra-aortic balloon bump.
morphine and with the novel approach of chewing or crushing the drug (Figure 3). It is evident that at least 2 hours are needed for the P2Y12 inhibitors to exert a significant platelet inhibition (PRU < 180), regardless of morphine administration. Consequently, at the onset of the coronary angiography P2Y12 inhibitors do not confer any protective effect and do not influence TIMI grade flow or spontaneous ST-segment resolution. Hence, the described negative association between morphine and both spontaneous reperfusion and TIMI flow grade (10-46 min after DAPT loading is essentially independent of its effect on P2Y12 inhibitors. This insight, along with numerous studies indicating a plausible association between morphine and suboptimal myocardial reperfusion,3,24,25 suggest that this association is possibly beyond the induced P2Y12-pharmacodynamic effect.

We have recently employed relevant in-vivo thrombosis models that confirmed for the first time a direct prothrombotic effect of morphine.5 Sheu et al previously confirmed morphine to potentiate both platelet aggregation and agonist-induced ATP release. This effect was stimulated in human platelets through α2 adrenoceptors.26 Activation of the α2A receptor on the platelet surface enhances thrombus stabilization under pathologic conditions.27

Study Limitations

This study is observational in nature and might be inherently prone to a variety of biases. Morphine administration was at the discretion of the health-givers. In the morphine group, we did not consider the precise dose of morphine assigned (as it was not readily available), as well as corresponding pain scales. The study is not powered to test the impact of morphine dose and exact timing on the different endpoints. No platelet function tests were done. Finally, this study was conducted in the years 2010-2013. It may not adequately reflect contemporary practice of morphine use, with the major advances recently introduced in acute cardiovascular pharmacology, primarily the new potent P2Y12 receptor inhibitors.

Conclusion

The downstream antiplatelet loading practice at our medical center, during the period of this study, obviously delayed platelet inhibition before PCI; although both groups, with and without morphine treatment, were comparable with respect to demographic and periprocedural characteristics, the protracted platelet hyper-responsiveness secondary to the downstream P2Y12 administration policy was associated with a negative outcome in the morphine group. Altogether, acknowledging possible role of morphine in halting optimal reperfusion indices, irrespective of its notorious role in delaying the action of P2Y12 inhibitors, it seems prudent to use morphine judiciously. Although the present study’s paradigm of no upstream P2Y12 inhibitors loading is not consistent with the current guidelines,28 and despite the high potency of the new P2Y12 receptor inhibitors, a potential implication of the current study is still relevant in selected populations where P2Y12 inhibitors absorption is impaired or delayed including emergently
intubated patients, those undergoing targeted temperature management, and cardiogenic shock patients. In the latter populations a bail-out administration of GP IIb/IIIa should be highly considered.

This report is only hypothesis generating and opens the door for a future prospective double blind randomized study, before a final conclusion can be definitively drawn about the use of morphine in patients with ST-elevation myocardial infarction.

Authors’ Note
This study was carried out at the Heart Institute, Hillel Yaffe Medical Center Affiliated with Rappaport Faculty of Medicine, Technion—Israel Institute of Technology, Haifa, Israel.

Author Contributions
Ariel Roguin and Ofer Kobo: Acquisition and analysis of the work; final approval, agreement to be accountable for all aspects of the work. Simcha Ron Meisel and Yaniv Levi: Analysis of the work; revising it critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work. Emad Maraga, Naama Amsalem and Rinat Malka: Acquisition and analysis of the work; agreement to be accountable for all aspects of the work. Aaron Frimerman: Conception/design and analysis of the work; revising it critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work. Rami Abu Fanne: Conception/design/acquisition and analysis of the work; drafting the work and revising it critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work.

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