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Editorial

Morphine in acute heart failure: Feeling better or living longer?

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The intravenous therapies introduced for Acute Heart Failure (AHF) have remained almost unchanged in the last decades [1], although increasing short and long-term safety concerns have been reported regarding the use of inotropes/vasopressors [2] and use of morphine [3,4].

Morphine continue to be used in the initial phase of Acute Pulmonary Oedema (APO) based on its beneficial hemodynamic effects (reduction in pre- and afterload) and those on the central nervous system (improvement in patient anxiety, respiratory difficulty and chest pain) [4]. Nonetheless, these beneficial effects may be outweighed by the presence of adverse effects, such as hypotension, a reduction in ventilatory effort, obnubilation, as well as nausea and vomiting with potential risk of aspiration [4]. Therefore, the use of morphine in APO is currently controversial, and numerous authors have warned about the potential negative impact of Morphine on the outcomes of patients.

In present manuscript, Caspi O et al investigated the effect of the early administration of morphine on clinical outcomes in a large cohort of AHF patients [5]. Patients treated by morphine after 24 h and patients treated with morphine for palliative reasons were excluded. Primary endpoints included in-hospital mortality and need of invasive mechanical ventilation (IMV). Secondary endpoints included non-invasive ventilation, need for inotropes and acute kidney injury (AKI). The association between morphine and the combined endpoint, one-year mortality/HF-readmissions, was evaluated in AHF patients who survived at discharge.

Of the total cohort of AHF patients, 5.5% patients were treated with morphine in the first 24 h following hospital admission.

Because the baseline characteristics of morphine-treated patients differed markedly from those not treated with morphine, propensity-score-matching using 26 clinical variables was generated. The final analytical cohort included 1344 AHF patients, as result of 672 patient pairs.

The results of this analysis [5] showed that incidence of IMV was higher in the morphine-treated patients than in matched patients in the no-morphine cohort (7.4 vs 3.6%; $p = 0.007$). In-hospital mortality was also higher in the morphine group than in the matched no-morphine group (17.4% vs 13.4%; $p = 0.024$).

For both endpoints, IMV and mortality, there was a significant linear dose-dependency (< and >5 mg) for the adverse effect of morphine, and furthermore when compared with the control group, the adjusted OR for mortality was 1.48 for patients receiving <5 mg of morphine and 1.96 for patients receiving >5 mg of morphine (p for trend = 0.008). In addition, morphine was associated with a significant increase of all secondary outcomes: non-invasive ventilation, inotrope use and AKI. The one-year Kaplan-Meier estimates for the combined endpoint of HF-readmission/death demonstrated no difference in one-year post-discharge event rates between the two groups (OR = 1.11;95%CI 0.93–1.33). In subgroup analysis, the effect of morphine on in-hospital mortality or need of IMV was similar regardless SBP, LVEF and lactate level.

The authors should be commended for providing contemporary data about the outcome of morphine treated patients in the setting of AHF. Previous studies describing the association between morphine and adverse outcome had serious limitations related to the methodology, uniformity of the study population, the lack of data regarding the dose, timing of use, and the reason for the use of Morphine [3,6,7].

Notably, the present study has several strengths: a relative uniform cohort of 92% APO patients, the largest number of pairs used in propensity-matching-score, selective inclusion criteria (only patients treated in the first 24 h and excluding patients treated as palliation), dose-dependent relationship of morphine with primary endpoints and data about long-term outcomes.

Distinct to previous studies using propensity-matching-score [3,7], the present study reports for the first time the significant risk for in-hospital mortality associated to morphine (Fig. 1). Association between morphine and in-hospital mortality was similar to other contemporary studies which investigated the effect of early morphine administration for relieving dyspnea and anxiety [3,7], and lower than in ADHERE study [6] where the timing and the reason of Morphine treatment were more diverse.

The lack of association between morphine and long-term outcomes implies that the negative effects of morphine are limited to the

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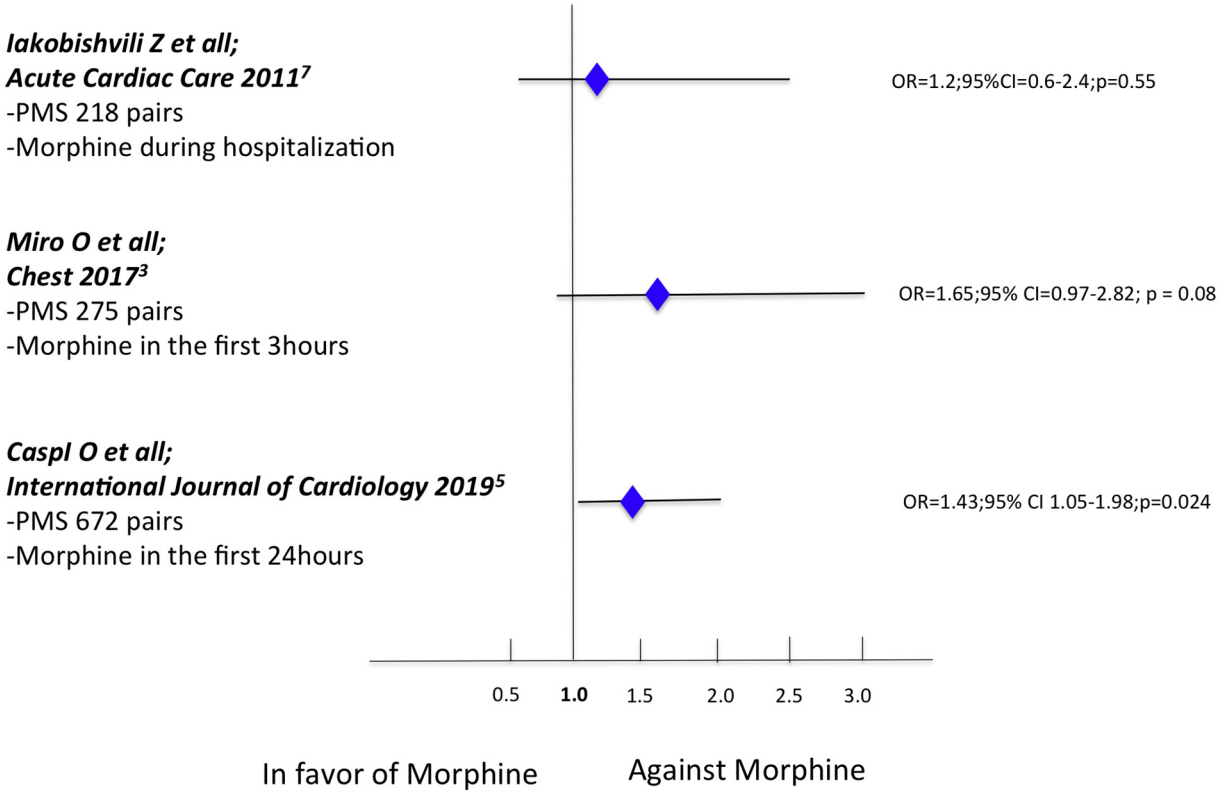

Fig. 1. Forest plot of in-hospital mortality in several AHF observational studies using propensity matching analysis by morphine vs no-morphine use. Abbreviations = CI = confidence interval; OR = odd ratio; PMS = propensity matching score.

hospitalization or to the first weeks post-discharge. These findings are similar to a recent study [3] exploring morphine associated risk of death at different time points during hospitalization and 30-days post-discharge, showing that the mortality risk gradually decreased over time.

Although the exact putative mechanism linking morphine treatment to in-hospital mortality is not clearly known, hemodynamic compromise and depression of central respiratory drive may contribute to the mortality excess associated to Morphine.

In an observational study [8], inotrope use and need of IMV were the most important independent predictors for in-hospital mortality in patients admitted with APO, suggesting delay in delivering appropriate care or direct adverse negative effects of these therapies. By relieving anxiety and respiratory distress, morphine may mask severe hypoxemia and may delay the initiation of IMV. Although the incidence of IMV was higher in morphine group, probably a substantial proportion of Morphine treated patients received IMV in extremis or as part of cardiopulmonary resuscitation.

Although, APO patients in settings of pEF or preserved SBP may have a lower incidence of negative hemodynamic effects, there is no reasonable justification to recommend morphine to these patients, since subgroup analysis showed similar hazard of death/need of intubation regardless baseline SBP or LVEF. However, inclusion of baseline levels of Natriuretic Peptides (NPs) in subgroup analysis would have been refined prognosis of these patients since NPs levels at admission are associated to short-term mortality [9].

In conclusion, Caspi et al, reported a significant association between morphine and in-hospital mortality [5]. These results are in the line with several other observational studies reporting potential harmful effects associated with Morphine [3,6,7]. However, it may not be reasonable to consider the safety and efficacy of morphine treatment in APO based only on previous retrospective studies, since simply, the association between morphine and mortality is not a proof for causal relationship. Furthermore, despite of using propensity-score-matching to minimize selection bias, residual confounding can never be fully excluded. Also, the quality of data coming from an observational study is lower than obtained in a properly monitored randomized clinical trial. Recently, a prospective, open-label, randomized study, the MIdazolan versus MOrphine in Acute Pulmonary Edema trial (MIMO-NCT02856698) was designed to evaluate efficacy and safety of Morphine in patients with APO [10]. MIMO trial will address our gaps in knowledge on the adverse effects and/or risks associated with morphine use in APO.

Declaration of Competing Interest

None.

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