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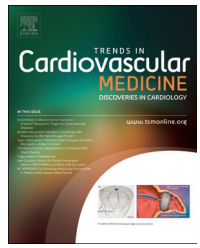

Time-honored treatments for the initial management of acute coronary syndromes: Challenging the status quo

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A B S T R A C T

Morphine, oxygen, and nitrates are time-honored therapies for the initial management of acute coronary syndrome (ACS). The traditional goal of these agents in ACS has been to (1) relieve symptoms, (2) prevent infarction or limit its size, and (3) improve outcomes, both acutely and during follow-up. Despite their ongoing use in routine ACS care, nitrates, morphine, and oxygen have no evidence of clinical outcomes benefit from randomized trials. Furthermore, emerging data have recently suggested that, in certain situations, morphine and oxygen may actually be associated with harm in the setting of ACS. In this review article, we thoroughly examine updated evidence for each of these acute-phase ACS agents with respect to their individual risks and benefits. We review guideline recommendations for these therapies and outline future directions for their use in clinical practice.

Key words: Morphine, Oxygen, Nitrates.

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Introduction

The use of morphine, oxygen, nitrates, and aspirin is often recommended as first-line therapy in patients with acute coronary syndromes (ACS). This strategy has often been summarized as "MONA" in many textbooks, websites, and in US teaching hospitals and medical training institutions that follow the UK tradition [1–10]. The traditional goal of these acute-phase ACS agents has been to (1) relieve symptoms, (2) prevent infarction or limit its size, and (3) improve outcomes, both acutely and during follow-up. However, emerging data have recently challenged the routine administration of these therapies in ACS. For example, morphine has been associated with increased mortality when administered to non-ST elevation myocardial infarction (NSTEMI) patients in observational cohorts, with mechanistic research further suggesting that morphine delays the gastrointestinal absorption of antiplatelet therapy [11,12]. In addition, oxygen has been associated with increased infarct size and arrhythmias when administered to non-hypoxic patients [13]. The data for nitrates are consistently inconclusive. Therefore, of the four common therapies administered in the initial management of ACS patients, aspirin is the only one with high-quality evidence for benefit. In this narrative review, we will examine the utility of morphine, oxygen, and nitrates in ACS, including the potential benefits and harmful effects of each, and reflect on the future of these agents in clinical practice.

Morphine

Morphine was recognized as a useful analgesic in the management of ACS as far back as 1930 [14]. Since then it has become the standard treatment for ACS patients with severe chest pain, with endorsements from the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and the European Society of Cardiology (ESC) [15,16]. However, concerns about morphine use have emerged over the past decade due to an observational association with adverse clinical outcomes in NSTEMI patients and a delay in the absorption of oral anti-platelet agents; placing its routine use under closer scrutiny [11,17–19] (Table 1).

Current guidelines

The ESC guidelines for the management of ST segment elevation myocardial infarction (STEMI), published in 2012, provide a Class 1 (level of evidence C) recommendation for morphine utility in STEMI patients (Table 2) [20]. In contrast, 2015 ESC NSTEMI guidelines, recommend morphine exclusively in the context of resistant chest pain after nitrate and beta blocker therapy administration and provide no formal class of recommendation [21].

The 2013 ACCF/AHA guidelines provide no formal class of recommendation or level of evidence designation for the utility of morphine in STEMI patients. However, they state that "In the absence of a history of hypersensitivity, morphine sulfate is the drug of choice for pain relief in patients with ST-segment elevation MI (STEMI)", as, "it can alleviate the work of breathing, reduce anxiety, and favorably affect ventricular loading conditions" [22]. The 2014 ACCF/AHA Guidelines for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes, provide a Class 2b recommendation (level of evidence B) for morphine administration in this cohort [23].

Benefits

Analgesia

Chest pain is the most common presenting complaint in ACS [24]. Analgesic options in this cohort remain limited and there have been few comparative trials. Morphine is the standard in ACS patients with pain refractory to beta blockers or nitrates. To take one example, in the Metoprolol-Morphine (MEMO) trial, among 265 adults with suspected or definite MI, morphine offered faster and more effective analgesia than metoprolol [25].

Hemodynamic effects

Morphine decreases heart rate, blood pressure, and venous return [26]. These effects appear to reduce myocardial oxygen demand during ACS. However, this hypothesis is only supported by two studies [26,27]. Unfortunately, both studies are limited by small numbers and neither occurred in the setting of ACS.

Concerns

Clinical outcomes

In 2005, a retrospective observational analysis of 57,039 NSTEMI patients found that morphine recipients had a significantly higher incidence of ST depression and positive cardiac biomarkers [11]. Furthermore, morphine recipients had a significantly higher likelihood of recurrent MI (odds ratio = 1.34), death (OR = 1.48), and the composite end point of both (OR = 1.44) [11]. Subsequently, de Waha et al. [28] reported that STEMI patients who received morphine were more likely to have a larger infarct and reduced myocardial salvage indices on cardiac MRI.

In contrast, two other, albeit smaller, observational studies failed to demonstrate adverse outcomes with morphine use in ACS [29,30]. Iakobishvili et al. used a propensity score to match 249 STEMI pairs and found that the rate of 30-day mortality appeared lower in those who received narcotics (2.4% vs. 6.2%, $p = 0.04$), with no statistically significant difference in outcomes between 95 matched NSTE-ACS patients ($p = 0.16$) [29]. Puymirat et al. [30] found that, after adjustment for baseline differences, a composite of in-hospital complications and 1-year survival (hazard ratio = 0.69; 95% confidence interval: 0.35–1.37) was not increased with pre-hospital morphine use in 2438 STEMI patients. After propensity score matching, 1-year survival according to pre-hospital morphine was also similar. However, in this study, the rate of non-fatal recurrent MI was higher in patients pre-treated with morphine (1.8 vs. 0.7%, $p = 0.03$) [30].

Interaction with anti-platelet agents

New data suggest that morphine may inhibit and delay the absorption of oral anti-platelet agents. This off-target effect