Association between pre-hospital chest pain severity and myocardial injury in ST elevation myocardial infarction: A post-hoc analysis of the AVOID study

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ABSTRACT

Background: We sought to determine if an association exists between prehospital chest pain severity and markers of myocardial injury.

Methods and Results: Patients with confirmed ST elevation myocardial infarction (STEMI) treated by emergency medical services were included in this retrospective cohort analysis of the AVOID study. The primary endpoint was the association of pre-hospital initial chest pain severity, cardiac biomarkers and infarct size based on cardiac magnetic resonance imaging. Groups were categorized based on moderate to severe chest pain (numerical rating scale pain ≥ 5/10) or less than moderate severity to compare procedural and clinical outcomes. 414 patients were included in the analysis. There was a weak correlation between initial pre-hospital chest pain severity and peak creatine kinase (r = 0.16, p = 0.001) and peak cardiac troponin I (r = 0.14, p = 0.005). Both were no longer significant after adjusting for known confounders. There was no association between moderate to severe chest pain on arrival and major adverse cardiac events at 6 months (20% vs. 14%, p=0.12). There was a weak correlation between history of ischemic heart disease (r = 0.16, p = 0.001), percutaneous coronary intervention (r = 0.16, p = 0.001), left anterior descending artery (r = 0.12, p = 0.012) as the culprit vessel and a weak negative correlation between age (r = -0.14, p = 0.039) and chest pain.

Conclusion: Only a weak association between pre-hospital chest pain severity and markers of myocardial injury was identified, supporting more judicious use of opioid analgesia with a focus on patient comfort.

1. Introduction

The goal of eradicating pain in a patient with ischemic chest pain has long been enshrined in medical and emergency medical service (EMS) education and training. This is at least partly due to early studies suggesting beneficial hemodynamic effects through reduced pain related sympathetic stimulation, venodilatory and vasodilatory effects [1]. Despite this, the clinical benefit of achieving “pain-free status” has never been evaluated in prospective studies. It has however, led to an approach where high doses of opioids are often used in the pre-hospital and in-hospital setting to achieve a pain-free state until definitive treatment in the form of reperfusion therapy is instituted. It has also led

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to pain reduction forming a key performance indicator for EMS [2]. 
Given the potential adverse cardiac effects of opioids due to the recently 
identified interaction between opioid analgesia and oral P2Y12 inhibitor 
therapy [3,4], and the integral role of oral P2Y12 inhibitor therapy in 
acute coronary syndrome (ACS) [5], we sought to assess whether pre-
hospital pain severity is associated with surrogate markers of myocar-
dial injury in patients with ST elevation myocardial infarction (STEMI). 
This was to explore whether there is a benefit of opioid analgesia in 
STEMI in addition to its analgesic effects for example through beneficial 
haemodynamic effects that have translated into improved markers of 
myocardial injury. Additionally, given the complex, subjective nature of 
pain, we sought to identify predictors of chest pain severity.

2. Methods

2.1. Study design

This study is an exploratory, secondary observational analysis of the 
Air Versus Oxygen In Myocardial Infarction (AVOID) trial. A detailed 
description of the AVOID study design and results has been previously 
published (NCT 01272713) [6,7]. Briefly, this was a prospective, 
multicenter, randomized controlled trial enrolling 638 patients with 
suspected STEMI between October 2011 and July 2014 transferred to 9 
Percutaneous Coronary Intervention (PCI) capable hospitals in Mel-
bourne, Australia. The original study was approved by ethics commit-
tees at each participating hospital with delayed written informed 
consent from the participant or next of kin obtained as soon as patients 
were stabilized in hospital.

2.2. Participants

Inclusion criteria for the AVOID study were patients 18 years or older 
with chest pain symptoms for < 12 h prior and a 12-lead electrocar-
diogram consistent with ST elevation. Exclusion criteria included hyp-
oxemia on room air (SpO2 < 94%), oxygen administration prior to 
randomization, altered conscious state or transport to a non-
participating hospital.

Opioid administration was guided by current Ambulance Victoria 
guidelines for management of ischemic chest pain. The guideline rec-
commended up to 5 mg of morphine or 50 µg of fentanyl intravenously 
every 5 min as required. Patients could also receive up to 200 µg of 
intranasal fentanyl every 5 min if intravenous access was not available. 
For this analysis, patients with cardiogenic shock and patients not 
receiving opioids were excluded.

2.3. Study outcomes

The AVOID study utilized highly correlated co-primary endpoints of 
peak troponin I (cTnI) and creatine kinase (CK) as surrogate markers of 
myocardial injury. Other secondary endpoints included ST-segment 
resolution, mortality and major adverse cardiac events (MACE) at hos-
pital discharge and 6 months. Cardiac Magnetic Resonance Imaging 
(MRI) was also performed at 6 months in a subset of 139 patients to 
measure infarct size.

The current analysis aimed to evaluate the association between chest 
pain as reported to paramedics using the 11 point numerical rating scale 
(NRS) at first contact and surrogate markers of myocardial injury such as 
peak creatine kinase (CK), peak troponin I (cTnI) and cardiac MRI 
derived infarct size.

Paramedics ascertained pain severity using the well validated NRS 
method for acute pain [8,9] which is part of standard paramedic 
assessment of patients with suspected STEMI. After the measurement at 
first contact, repeat pain scores using NRS were measured at approxi-
ately 5 min intervals until hospital arrival. Pain scores were always 
observed prior to initial opioid administration and subsequent dosing. 
We also evaluated the association between initially reported chest 
pain severity and clinical endpoints and the patient characteristics that 
predicted initial chest pain severity.

For the analysis, total opioid dose was calculated by converting the 
fentanyl dose (intravenous or intranasal) into an equivalent morphine 
dose by multiplying total dose by 100 and adding this to the total 
morphine dose if both drugs were used. 
We defined moderate to severe chest pain as a NRS of at least 5 out of 
10 as previously described [10–12].

We also undertook sensitivity analyses comparing outcomes for pa-
tients with severe chest pain (NRS 8–10) compared to those that did not 
and also for patients that were pain-free on arrival to hospital (NRS 0) 
compared to those that were not.

2.4. Statistical analysis

All statistical analysis was performed using SPSS version 22 (IBM). 
Variables approximating a normal distribution were summarized as 
mean ± SD and groups were compared using analysis of variance. Non-
normally distributed variables were summarized as median and third 
quartiles (Q1, Q3) and compared using Wilcoxon rank sum test. Bino-
mial variables were expressed as proportions and 95% confidence in-
tervals and compared using Chi-Square tests.

Spearman rank correlation was used to evaluate the relationship 
between initial pain NRS scores and cardiac biomarkers and MRI mea-
sures of infarct size. We utilized linear regression to evaluate the rela-
tionship between chest pain severity on arrival and markers of 
myocardial injury whilst adjusting for potential confounding factors. A 
log transformation of the biomarker and infarct size based on cardiac 
MRI data significantly improved the normality of residuals and therefore 
this was undertaken before inclusion in the linear regression model. We 
utilized Spearman rank correlation to identify predictors of initial chest 
pain on EMS arrival. We also used binary logistic regression to assess the 
association between moderate to severe initial chest pain and rates of 6 
month MACE after adjusting for known confounders. Identifiable data 
underlying this article cannot be shared publicly due to the need to 
maintain the privacy of individuals that participated in the study. De-
identified data will be shared on reasonable request to the correspond-
ing author. The first author had full access to the data in the study and 
takes responsibility for its integrity and the data analysis.

3. Results

Of the 638 patients enrolled in the AVOID trial, 441 patients were 
confirmed to have STEMI after emergent coronary angiography. Only 18 
patients with confirmed STEMI were not administered opioids and 
therefore these patients and 9 patients without available pain scores 
were also excluded. A total of 414 patients were included in this anal-
ysis, with confirmed STEMI undergoing PCI and available pain scores.

Patients with moderate to severe chest pain were significantly 
younger (61 vs. 65 years of age, p = 0.016), had a higher body mass 
index (BMI) (27.8 vs. 27.3 kg/m², p = 0.027), higher rates of dyslipi-
demia (59% vs. 44%, p = 0.004), ischemic heart disease (22% vs. 10%, 
p = 0.005) and previous PCI (15% vs. 4%, p = 0.001) (see Table 1).

Baseline medical therapy was similar between the two groups with 
the exception of aspirin (24% vs. 13%, p = 0.016) which was higher in 
the moderate to severe chest pain group (see supplementary table 1).

In the prehospital setting, there was greater administration of sub-
lingual or topical GTN (27% vs. 15%, p < 0.001) in patients with 
moderate to severe chest discomfort. There was greater use of opioids 
in this group as well (15 mg IV morphine equivalent vs. 10 mg, p < 0.001). 
The respiratory rate was higher in patients with moderate to severe chest 
discomfort (18 respirations per minute vs. 16, p < 0.001). Patients had 
greater pain reduction (5 vs. 3 points NRS, p < 0.001) but higher final 
pain scores (3 vs. 1 points NRS, p < 0.001) in patients with moderate to 
severe initial pain (see Table 2).

With respect to interventional characteristics, the left anterior
no difference in left ventricular ejection fraction or infarct size based on cardiac MRI across initial pain groups (see Table 3). There was a significant but weak correlation between severity of chest pain on arrival and log transformed peak CK (β coefficient = 0.039, 95% CI: 0.017 to 0.061, p = 0.012) and the left anterior descending artery as the culprit artery (r = -0.12). All-cause mortality at hospital discharge and 6 month follow-up was no different between the groups (see supplementary table 3). Rates of MACE at 6 months were no different between the groups (20% vs. 14%, p = 0.12).

We utilized Spearman rank correlation to evaluate potential predictors of initial chest pain severity on arrival including age, sex, history of smoking, ischemic heart disease, diabetes, hypertension, cerebrovascular disease, dyslipidemia, peripheral vascular disease, LAD as culprit artery and pre-PCI TIMI flow. There was a weak negative correlation between age and initial chest pain severity (r = -0.1, p = 0.039). Presence of ischemic heart disease (r = 0.16, p = 0.001), PCI (r = 0.16, p = 0.001) and the left anterior descending artery as the culprit artery (r = 0.12, p = 0.012) were all weakly correlated with initial chest pain severity.

Additionally, we performed a sensitivity analysis of patients with severe (NRS ≥ 7) initial pain compared to not severe pain. Higher peak C-TnI and CK levels in those with severe chest discomfort was seen similar to the overall analysis (see supplementary table 4) but no association was seen between severe chest discomfort and clinical outcomes (see supplementary table 5).

A sensitivity analysis of patients that were pain-free on hospital arrival (NRS 0) compared to those that were not was also conducted. Patients with zero pain were administered significantly lower doses of opioids (median dose 10 mg vs 13 mg, p < 0.001, see supplementary table 6) in the prehospital setting. They also had lower initial pain scores (NRS 5 vs. 8, p < 0.001) with greater pain reduction (NRS 5 vs. 4, p < 0.001) in the prehospital setting. Patients with zero pain on hospital arrival had significantly lower rates of TIMI 0/1 flow pre-PCI (77% vs. 91%, p < 0.001) and shorter door to intervention times (median time 50

### Table 3

| Markers of myocardial injury and chest pain severity. | Chest pain at least 5/10 | P value
|-----------------------------------------------------|--------------------------|---------|
| Peak cTnI (µg/L) | 47 (19,130) | 82 (26,145) | 0.033 |
| Peak CK (U/L) | 1592 (782,3161) | 2093 (1031,3777) | 0.012 |
| LVEF % median (IQR) | 56 (50,52) | 54 (46,61) | 0.46 |
| Infarct size % median (IQR) | 15 (7,26) | 18 (8,29) | 0.49 |
| Infarct size proportion of LV mass % | 11 (5,16) | 10 (6,18) | 0.64 |

Table 4

| Spearman’s correlation - r value | P value |
|----------------------------------|---------|
| Peak cTnI | 0.14 | 0.005 |
| Peak CK | 0.16 | 0.001 |
| CMRI infarct size | 0.16 | 0.08 |

cTnI = cardiac troponin I, CK = creatine kinase, EDV = end-diastolic volume, IQR = interquartile range, LVEF = Left ventricular ejection fraction, LV = left ventricle.
vs. 56 min, $p = 0.019$ see supplementary table 7). Left ventricular ejection fraction assessed by cardiac MRI was higher in patients with zero pain on hospital arrival and infarct size as a proportion of left ventricular mass was also smaller in this group (see supplementary table 8). There was no difference in all-cause mortality or MACE at hospital discharge or 6 month follow-up between patients with zero pain on hospital arrival and those that did not (see supplementary table 9).

4. Discussion

We found a weak correlation between chest pain severity on arrival of EMS in the prehospital setting and creatine kinase and cardiac troponin I as surrogate markers of myocardial injury. We found no association between moderate to severe chest discomfort and recurrent MACE at 6 months. Lastly, we found no strong predictors of pre-hospital initial chest pain severity in patients with STEMI. Our sensitivity analyses also found an association between severe chest pain and myocardial injury based on cardiac biomarkers but not clinical outcomes. Additionally, zero chest pain on hospital arrival was not associated with clinical outcomes but rather was associated with reduced markers of myocardial injury likely explained by improved antegrade flow in the culprit coronary artery in this group. This also likely explains the achievement of zero pain on hospital arrival with lower opioid doses compared to patients with greater than zero pain scores on hospital arrival. These findings are supported by prior research demonstrating that reperfusion of ischemic myocardium significantly reduces the need for opioid analgesia and the duration of chest pain [13].

Achieving significant pain reduction is now enshrined even in government reporting requirements. For example, pain reduction in ischemic chest pain is a key performance indicator (KPI) for Ambulance services throughout Australia [2]. To meet this KPI, pain must be reduced by at least 2 points on the NRS between initial pain score on EMS arrival and final pain score at hospital handover. This leads to administration of significant opioid doses in the prehospital setting. The latter is of significant concern given there is now very convincing biochemical evidence that opioid analgesia impairs the bioavailability and subsequent antplatelet effect of all oral P2Y$_{12}$ inhibitors [4,14–20,35]. This exacerbates the delayed onset of platelet inhibition seen in patients with ST elevation myocardial infarction where therapeutic inhibition may only occur 4 or more hours after oral loading of P2Y$_{12}$ inhibitors [21–23]. Retrospective studies have suggested that administration of higher opioid doses may be associated with poorer outcomes although prospective randomized trials are required to confirm these findings as results are conflicting [3,24–27].

Whilst peak CK and cTnI was higher in patients with moderate to severe chest pain, there was a greater proportion of patients with anterior STEMIs in this group which likely confounds this association. Interestingly, we did not find any strong predictors of chest pain severity on EMS arrival. This likely reflects the subjective, complex nature and characteristics of pain where the severity of pain has not been able to predict patients having an ACS compared to those with non-ischemic chest pain [28,29]. Anterior infarcts where there is perhaps a greater proportion of myocardium in jeopardy was weakly correlated with chest pain severity as was a history of ischemic heart disease. However, previous studies have also suggested that the extent of the ischemic tissue in myocardial infarction is not the dominant contributor to pain response [30]. Younger patients also reported greater pain severity although this was also only weakly correlated but is consistent with previous studies suggesting older age is associated with lower pain scores and a greater risk for painless myocardial infarction [31].

Fig. 1. Spearman rank correlation between initial chest pain and markers of myocardial injury. Panel A plots correlation between initial chest pain based on numerical rating scale (NRS) on x axis and peak creatine kinase in U/L on y axis (CK). Panel B plots correlation between initial chest pain based on numerical rating scale (NRS) on x axis and peak cardiac troponin I in µg/L on y axis (CK). Panel C plots correlation between initial chest pain based on numerical rating scale (NRS) on x axis and infarct size in g based on cardiac MRI assessment on y axis.
studies have also suggested that diabetic patients have lower analgesic requirements with myocardial infarction however we did not identify this association in our study [32].

We believe our findings, in conjunction with growing concerns regarding the role of opioids in ACS, suggest a re-evaluation of the goals of chest pain management in the pre-hospital setting and the associated key performance indicators. Rather than aiming to achieve zero pain which may require the administration of high opioid doses, a focus on maintaining patient comfort in the prehospital setting until revascularization is achieved is preferable. This is also in line with current ESC guidelines supporting more judicious use of opioid analgesia in STEMI due to the potential interaction with oral P2Y12 inhibitors [33]. Additionally, future research should focus on evaluating the efficacy of non-opioid analgesia to achieve patient comfort in STEMI. To this end, we have undertaken a prehospital trial testing the safety and efficacy of intravenous lidocaine compared to intravenous fentanyl as analgesia in STEMI [34].

4.1. Limitations

There are several limitations of our study. This is a post-hoc analysis of a randomized controlled trial, therefore this analysis is hypothesis generating however we believe it is an appropriate study design to evaluate the association between chest pain severity and markers of myocardial injury. We also utilized CK and cardiac troponin I which are surrogate markers of myocardial injury with only a subset of patients where cardiac MRI evaluation of infarct size was available to determine correlation between prehospital pain severity and infarct size. Additionally, all patients in this analysis received opioid analgesia therefore, the impact of opioids on the association between chest pain severity and myocardial injury is limited, however we believe this reflects real-world international practice. Our study was limited to patients with confirmed STEMI and therefore is less generalizable to patients with non-STEMI where pain may be more transient or responsive to lower doses of analgesia. We also excluded patients with cardiogenic shock and out-of-hospital cardiac arrest which limits interpretability to this population.

The limitations of the original AVOID study also apply to this analysis namely the limited application of cardiac MRI, lack of a central core laboratory for assessment of biomarkers and incomplete cardiac troponin I (8.2%) and creatine kinase (0.5%) assessments in the study population. Given the relatively small sample size of the AVOID study, the current analysis is under-powered to evaluate clinical endpoints.

5. Conclusions

Our study suggests that the association between prehospital chest pain severity and markers of myocardial injury in STEMI is weak at best. Given that aiming for zero pain may lead to the administration of higher opioid doses, which may be detrimental, our data indicates that analgesia should be prescribed to achieve patient comfort rather than a pain-free state. Additionally, investigation of non-opioid analgesia for patients with STEMI to achieve patient comfort is warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Competing interests

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcha.2021.100899.

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