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 $\geq$ 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

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 $P2Y_{12}$ inhibitor therapy [3,4], and the integral role of oral $P2Y_{12}$ inhibitor therapy in acute coronary syndrome (ACS) [5], we sought to assess whether prehospital pain severity is associated with surrogate markers of myocardial 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 Melbourne, Australia. The original study was approved by ethics committees 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 electrocardiogram consistent with ST elevation. Exclusion criteria included hypoxemia 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 recommended 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 hospital 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 approximately 5 min intervals until hospital arrival. Pain scores were always obtained 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 patients 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. Nonnormally distributed variables were summarized as median and third quartiles (Q1, Q3) and compared using Wilcoxon rank sum test. Binomial variables were expressed as proportions and 95% confidence intervals 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 measures of infarct size. We utilized linear regression to evaluate the relationship 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. Deidentified data will be shared on reasonable request to the corresponding 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 analysis, 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 = 0.001), had a higher body mass index (BMI) (27.8 vs. 27.3 kg/m2, p = 0.027), higher rates of dyslipidemia (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) use which was higher in the moderate to severe chest pain group (see supplementary table 1).

In the prehospital setting, there was greater administration of sublingual 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

Table 1

Baseline characteristics in patients with at least moderate initial chest pain compared to those with chest pain<5/10.

Baseline characteristics	Chest pain<5/10 N = 134	Chest pain at least 5/10 N = 280	P value
Age in years, mean (SD)	65 (12)	61 (12)	0.001
Male, n (%)	109 (81)	222 (79)	0.63
Diabetes n (%)	20 (15)	48 (17)	0.57
Hypertension n (%)	70 (52)	166 (59)	0.18
Dyslipidaemia n (%)	59 (44)	166 (59)	0.004
BMI kg/m2 Median (IQR) (n = 271)	27.3 (24,29)	27.8 (25,31)	0.027
Current or ex-smoking n (%) (n = 411)	86 (64)	202 (73)	0.07
PVD n (%)	5 (4)	7 (3)	0.49
CVD n (%)	11 (8)	12 (4)	0.1
IHD n (%)	14 (10)	61 (22)	0.005
Previous PCI n (%)	5 (4)	43 (15)	0.001
Previous CABGs n (%)	3 (2)	4 (1)	0.55
Heart Failure n (%)	4 (3)	7 (3)	0.77
Creatinine > 120 μmol/L n (%)	13 (10)	19 (7)	0.3
Symptom to intervention time in mins (IQR) N = 406	160 (127,240)	154 (126,225)	0.17
Prehospital duration time in mins (IQR) N = 406	105 (79,162)	97 (70,150)	0.12

BMI = body mass index, IQR = interquartile range, PVD = peripheral vascular disease, CVD = cerebrovascular disease, IHD = ischemic heart disease, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft surgery.

Table 2

Pre hospital characteristics.

Pre-hospital characteristics	Chest pain<5/10 N = 134	Chest pain at least 5/10 N = 280	P value
Status on arrival of paramedics			
Median HR (beats per minute) median (IQR)	73 (63,86)	76 (64,88)	0.3
Median SBP (mmHg) median (IQR)	130 (113,145)	134 (117,150)	0.21
Median oxygen saturation % (IQR) n = 412	99 (98,100)	99 (97,100)	0.23
Supplemental oxygen n % N = 412	66 (49)	146 (53)	0.54
GTN given n (%)	20 (15)	75 (27)	<0.001
Opioid units administered median (IQR)	10 (7.5,12.5)	15 (10,20)	<0.001
Respiratory rate on hospital arrival (per minute) Median (IQR) n = 408	16 (16,18)	18 (16,20)	<0.001
Initial GCS median (IQR) n = 408	15	15	0.34
Final pain score NRS median (IQR)	1 (0,2)	3 (1,4)	<0.001
Pain reduction NRS median (IQR)	3 (1,4)	5 (4,6)	<0.001

HR = heart rate, IQR = interquartile range, SBP = systolic blood pressure, GCS = Glasgow coma scale, GTN = glyceryl trinitrate, NRS = numerical rating scale.

Table 3

Markers of myocardial injury and chest pain severity.

Markers of myocardial injury	Chest pain<5/10 N = 134	Chest pain at least 5/10 N = 280	P value
Peak cTnI μg/L median (IQR)	47 (19,130)	82 (26,145)	0.033
Peak CK U/L median (IQR)	1592 (782,3161)	2093 (1031,3777)	0.012
LVEF % median (IQR)	56 (50,62)	54 (46,61)	0.46
Infarct size g median (IQR)	15 (7,26)	18 (8,29)	0.49
Infarct size proportion of LV mass % Median (IQR)	11(5,16)	10 (6,18)	0.64

cTnI = cardiac troponin I, CK = creatine kinase, EDV = end-diastolic volume, IQR = interquartile range, LVEF = Left ventricular ejection fraction, LV = left ventricle.

0.001) as well as peak cardiac troponin I (r = 0.14, p = 0.005) as markers of myocardial injury. There was no significant correlation between initial chest pain score and cardiac MRI measurement of infarct size (see Table 4) and Fig. 1. After adjusting for other confounding factors such as age, sex, BMI, history of dyslipidemia, smoking, ischemic heart disease and symptom to intervention time, the correlation between chest pain on arrival and log transformed peak CK (β coefficient 0.092, 95% CI −0.014, 0.095, p = 0.144) and cardiac troponin I (β coefficient 0.066, 95% CI −0.039, 0.117, p = 0.331) were no longer significant.

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 8–10) initial pain compared to not severe pain. Higher peak cTnI 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

descending (LAD) artery as the culprit vessel was more frequent (41% vs. 24%, p = 0.001) in the moderate to severe chest pain group. TIMI flow pre-PCI, procedural success, symptom and door to intervention times were similar between the groups (see supplementary table 2).

Peak creatine kinase (2093 vs. 1592 U/L, p = 0.012) and peak cardiac troponin I (82 vs. 47 ng/L, p = 0.033) were both significantly higher in patients with moderate to severe initial chest pain. There was 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 of EMS and peak creatine kinase (r = 0.16, p =

Table 4

Correlation between chest pain on arrival and markers of myocardial injury.

Spearman's correlation – r value	Chest pain on arrival	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, CMR = cardiac magnetic resonance Imaging.
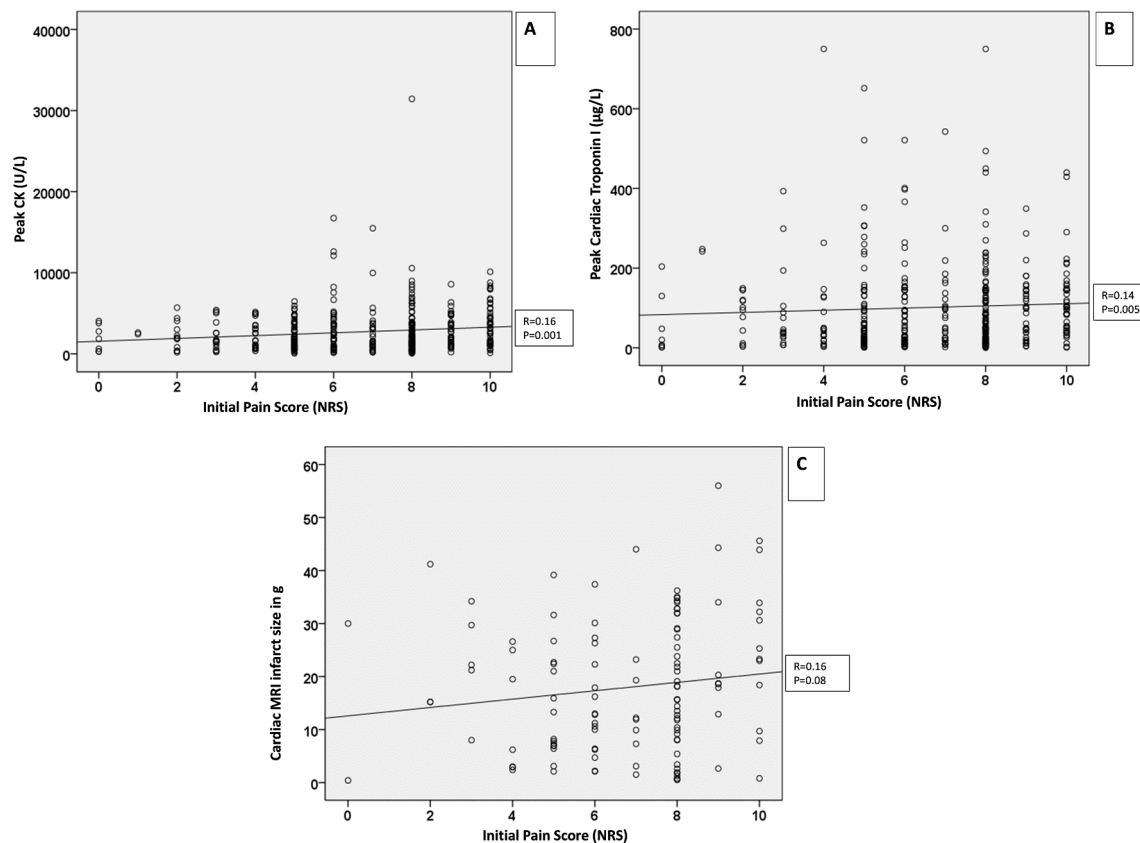
Fig. 1. Spearman rank correlation between initial chest pain and markers of myocardial injury. Panel A plots correlation between initial chest pain based on numerical rating scale (NRS) on x axis and peak creatine kinase in U/L on y axis (CK). Panel B plots correlation between initial chest pain based on numerical rating scale (NRS) on × 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 × axis and infarct size in g based on cardiac MRI assessment on y axis.

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 antiplatelet 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]. Prior

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 P2Y$_{12}$ 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.

Appendix A. Supplementary data

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

References

[1] J.J. Rouby, B. Eurin, P. Glaser, J.J. Guillosson, J. Nafziger, R. Guesde, P. Viars, Hemodynamic and metabolic effects of morphine in the critically ill, Circulation. 64 (1) (1981) 53–59, https://doi.org/10.1161/01.CIR.64.1.53.

[2] Statement of Priorities: 2019-2020 Agreement between the Minister for Ambulance Services and Ambulance Victoria, (2019). https://www2.health.vic.gov.au/hospitals-and-health-services/fundingperformance- accountability/statement-of-priorities (accessed March 29, 2021).

[3] T.J. Meine, M.T. Roe, A.Y. Chen, M.R. Patel, J.B. Washam, E.M. Ohman, W. F. Peacock, C.V. Pollack, W.B. Gibler, E.D. Peterson, Association of intravenous morphine use and outcomes in acute coronary syndromes: Results from the CRUSADE Quality Improvement Initiative, Am. Heart J. 149 (6) (2005) 1043–1049, https://doi.org/10.1016/j.ahj.2005.02.010.

[4] H. Fernando, J.A. Shaw, P.S. Myles, K. Peter, D. Stub, The opioid-P2Y12 inhibitor interaction: Potential strategies to mitigate the interaction and consideration of alternative analgesic agents in myocardial infarction, Pharmacol. Ther. 217 (2021) 107665, https://doi.org/10.1016/j.pharmthera.2020.107665.

[5] H. Fernando, J.D. McFadyen, J. Palasubramaniam, J. Shaw, X. Wang, D. Stub, K. Peter, Antithrombotic Therapy in Myocardial Infarction: Historic Perils and Current Challenges—A 70-Year Journey, Thromb Haemost. 120 (2020) 1352–1356.

[6] D. Stub, K. Smith, S. Bernard, Z. Nehme, M. Stephenson, J.E. Bray, P. Cameron, B. Barger, A.H. Ellims, A.J. Taylor, I.T. Meredith, D.M. Kaye, Air versus oxygen in ST-segment-elevation myocardial infarction, Circulation. 131 (24) (2015) 2143–2150, https://doi.org/10.1161/CIRCULATIONAHA.114.014494.

[7] D. Stub, K. Smith, S. Bernard, J.E. Bray, M. Stephenson, P. Cameron, I. Meredith, D. M. Kaye, A randomized controlled trial of oxygen therapy in acute myocardial infarction Air Verses Oxygen in myocarDial infarction study (AVOID Study), Am. Heart J. 163 (3) (2012) 339–345.e1, https://doi.org/10.1016/j.ahj.2011.11.011.

[8] P.E. Bijur, C.T. Latimer, E.J. Gallagher, Validation of a Verbally Administered Numerical Rating Scale of Acute Pain for Use in the Emergency Department, Acad. Emerg. Med. 10 (4) (2003) 390–392, https://doi.org/10.1111/acem.2003.10.issue-410.1111/j.1553-2712.2003.tb01355.x.

[9] P.A. Jennings, P. Cameron, S. Bernard, Measuring acute pain in the prehospital setting, Emerg. Med. J. 26 (8) (2009) 552–555, https://doi.org/10.1136/emj.2008.062539.

[10] G. Andrieu, H. Amrouni, E. Robin, B. Carnaille, J.M. Wattier, F. Pattou, B. Vallet, G. Lebuffe, Analgesic efficacy of bilateral superficial cervical plexus block administered before thyroid surgery under general anaesthesia, Br. J. Anaesth. 99 (4) (2007) 561–566, https://doi.org/10.1093/bja/aem230.

[11] W. Mei, M. Seeling, M. Franck, F. Radtke, B. Brantner, K.-D. Wernecke, C. Spies, Independent risk factors for postoperative pain in need of intervention early after awakening from general anaesthesia., Eur. J. Pain Lond. Engl. 14 (2010) 149.e1–7. Doi: 10.1016/j.ejpain.2009.03.009.

[12] B.A. Williams, M.L. Kentor, M.T. Vogt, J.J. Irrgang, M.T. Bottegal, R.V. West, C. D. Harner, F.H. Fu, J.P. Williams, Reduction of verbal pain scores after anterior cruciate ligament reconstruction with 2-day continuous femoral nerve block: a randomized clinical trial, Anesthesiology. 104 (2006) 315–327, https://doi.org/10.1097/00000542-200602000-00018.

[13] J.H. Christensen, H.T. Sørensen, S.E. Rasmussen, L. Ravn, F.E. Nielsen, The effect of streptokinase on chest pain in acute myocardial infarction, Pain. 46 (1991) 31–34, https://doi.org/10.1016/0304-3959(91)90030-2.

[14] E.-L. Hobl, B. Reiter, C. Schoergenhofer, M. Schwameis, U. Derhaschnig, J. Kubica, T. Stimpfl, B. Jilma, Morphine decreases ticagrelor concentrations but not its antiplatelet effects: A randomized trial in healthy volunteers, Eur. J. Clin. Invest. 46 (1) (2016) 7–14, https://doi.org/10.1111/eci.12550.

[15] E.-L. Hobl, B. Reiter, C. Schoergenhofer, M. Schwameis, U. Derhaschnig, I.M. Lang, T. Stimpfl, B. Jilma, Morphine interaction with prasugrel: a double-blind, cross-over trial in healthy volunteers, Clin. Res. Cardiol. 105 (4) (2016) 349–355, https://doi.org/10.1007/s00392-015-0927-z.

[16] E.L. Hobl, T. Stimpfl, J. Ebner, C. Schoergenhofer, U. Derhaschnig, R. Sunder-Plassmann, P. Jilma-Stohlawetz, C. Mannhalter, M. Posch, B. Jilma, Morphine

decreases clopidogrel concentrations and effects: A randomized, double-blind, placebo-controlled trial, J. Am. Coll. Cardiol. 63 (2014) 630–635, https://doi.org/10.1016/j.jacc.2013.10.068.

[17] K. Ibrahim, R. Shah, R. Goli, T. Kickler, W. Clarke, R. Hasan, R. Blumenthal, D. Thiemann, J. Resar, S. Schulman, J. McEvoy, Fentanyl Delays the Platelet Inhibition Effects of Oral Ticagrelor: Full Report of the PACIFY Randomized Clinical Trial, Thromb. Haemost. 118 (08) (2018) 1409–1418, https://doi.org/10.1055/s-0038-1666862.

[18] J. Kubica, P. Adamski, M. Ostrowska, J. Sikora, J.M. Kubica, W.D. Sroka, K. Stankowska, K. Buszko, E.P. Navarese, B. Jilma, J.M. Siller-Matula, M. P. Marszałł, D. Rość, M. Koziński, Morphine delays and attenuates ticagrelor exposure and actioninpatients with myocardial infarction: The randomized, double-blind, placebo-controlled IMPRESSION trial, Eur. Heart J. 37 (3) (2016) 245–252, https://doi.org/10.1093/eurheartj/ehv547.

[19] J. Kubica, A. Kubica, B. Jilma, P. Adamski, E.L. Hobl, E.P. Navarese, J.M. Siller-Matula, A. Dąbrowska, T. Fabiszak, M. Koziński, P.A. Gurbel, Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors, Int. J. Cardiol. 215 (2016) 201–208, https://doi.org/10.1016/j.ijcard.2016.04.077.

[20] N.B. Senguttuvan, F. Suman, T. Paneerselvam, B. Malepati, S. Ramesh, M. V. Vallivedu, P. Badimela, M. Ramadoss, M. Iyer, P. Krishnamurthy, B. Vinod Kumar, J.V. Balasubramaniyan, S. Sadhanandham, R. Jebaraj, P. Manokar, T. R. Muralidharan, J.S. Murthy, S. Thanikachalam, P. Krishnamoorthy, U. Baber, G. Karthikeyan, Comparison of the effect of Morphine and Fentanyl in patients with acute coronary syndrome receiving Ticagrelor - The COMET (Comparison Morphine, Fentayl and Ticagrelor) randomized controlled trial, Int. J. Cardiol. 330 (2021) 1–6, https://doi.org/10.1016/j.ijcard.2021.02.037.

[21] G. Parodi, B. Bellandi, R. Valenti, A. Migliorini, 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, Am. Heart J. 167 (2014) 909–914, https://doi.org/10.1016/j.ahj.2014.03.011.

[22] A.A.C.M. Heestermans, J.W. van Werkum, D. Taubert, T.H. Seesing, N. von Beckerath, C.M. Hackeng, E. Schömig, F.W.A. Verheugt, J.M. ten Berg, Impaired bioavailability of clopidogrel in patients with a ST-segment elevation myocardial infarction, Thromb. Res. 122 (6) (2008) 776–781, https://doi.org/10.1016/j.thromres.2008.01.021.

[23] A.H. Tavenier, R.S. Hermanides, E. Fabris, D.J. Angiolillo, A.W.J. van 't Hof, Bridging the gap: Current and future insights for improving suboptimal platelet inhibition in STEMI, Int. J. Cardiol. 328 (2021) 40–45, https://doi.org/10.1016/j.ijcard.2020.11.042.

[24] B. Bellandi, C. Zocchi, I. Xanthopoulou, F. Scudiero, R. Valenti, A. Migliorini, D. Antoniucci, N. Marchionni, D. Alexopoulos, G. Parodi, Morphine use and myocardial reperfusion in patients with acute myocardial infarction treated with primary PCI, Int. J. Cardiol. 221 (2016) 567–571, https://doi.org/10.1016/j.ijcard.2016.06.204.

[25] Himawan Fernando, Ziad Nehme, Karlheinz Peter, Stephen Bernard, Michael Stephenson, Janet Bray, Peter Cameron, Andris Ellims, Andrew Taylor, David M Kaye, Karen Smith, Dion Stub, Prehospital opioid dose and myocardial

[26] Ji Quan Samuel Koh, Himawan Fernando, Karlheinz Peter, Dion Stub, Opioids and ST Elevation Myocardial Infarction: A Systematic Review, Heart Lung Circ. 28 (5) (2019) 697–706, https://doi.org/10.1016/j.hlc.2018.12.015.

injury in patients with ST elevation myocardial infarction, Open Heart. 7 (2) (2020) e001307, https://doi.org/10.1136/openhrt-2020-001307.

[27] Cian P. McCarthy, Vijeta Bhambhani, Eugene Pomerantsev, Jason H. Wasfy, In-hospital outcomes in invasively managed acute myocardial infarction patients who receive morphine, J. Intervent. Cardiol. 31 (2) (2018) 150–158, https://doi.org/10.1111/joic.v31.210.1111/joic.12464.

[28] B. Eriksson, D. Vuorisalo, C. Sylvén, Diagnostic potential of chest pain characteristics in coronary care, J. Intern. Med. 235 (1994) 473–478, https://doi.org/10.1111/j.1365-2796.1994.tb01105.x.

[29] S.M. Horner, Chest pain — no difference in severity between those having a myocardial infarction and chest pain from other causes, Int. J. Cardiol. 24 (3) (1989) 371–372, https://doi.org/10.1016/0167-5273(89)90020-X.

[30] M. Granot, P. Dagul, W. Darawsha, D. Aronson, Pain modulation efficiency delays seeking medical help in patients with acute myocardial infarction, PAIN. 156 (2015). https://journals.lww.com/pain/Fulltext/2015/01000/Pain_modulation_efficiency_delays_seeking_medical.24.aspx.

[31] M. Granot, R. Khoury, G. Berger, N. Krivoy, E. Braun, D. Aronson, Z.S. Azzam, Clinical and experimental pain perception is attenuated in patients with painless myocardial infarction, PAIN®. 133 (2007) 120–127, https://doi.org/10.1016/j.pain.2007.03.017.

[32] F.E. Nielsen, P. Gram-Hansen, J.H. Christensen, H.T. Sørensen, I.C. Klausen, L. Ravn, Reduced consumption of analgesics in patients with diabetes mellitus admitted to hospital for acute myocardial infarction, Pain. 47 (1991) 325–328, https://doi.org/10.1016/0304-3959(91)90223-K.

[33] B. Ibanez, S. James, S. Agewall, M.J. Antunes, C. Bucciarelli-Ducci, H. Bueno, A.L. P. Caforio, F. Crea, J.A. Goudevenos, S. Halvorsen, G. Hindricks, A. Kastrati, M.J. Lenzen, E. Prescott, M. Roffi, M. Valgimigli, C. Varenhorst, P. Vranckx, P. Widimský, ESC Scientific Document Group, 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Socie, Eur. Heart J. 39 (2018) 119–177. Doi: 10.1093/eurheartj/ehx393.

[34] Himawan Fernando, Catherine Milne, Ziad Nehme, Jocasta Ball, Stephen Bernard, Michael Stephenson, Paul S. Myles, Janet E. Bray, Jeffrey Lefkovits, Danny Liew, Karlheinz Peter, Angela Brennan, Diem Dinh, Emily Andrew, Andrew J. Taylor, Karen Smith, Dion Stub, An open-label, non-inferiority randomized controlled trial of lidocAine Versus Opioids In MyocarDial Infarction study (AVOID-2 study) methods paper, Contemp. Clin. Trials. 105 (2021) 106411, https://doi.org/10.1016/j.cct.2021.106411.

[35] Himawan Fernando, Thy Duong, Kevin Huynh, Jonathan Noonan, James Shaw, Stephen J Duffy, Ziad Nehme, Karen Smith, Paul Myles, Peter Meikle, Karlheinz Peter, Dion Stub, Effects of lignocaine vs. opioids on antiplatelet activity of ticagrelor: the LOCAL trial, Eur. Heart J. 42 (39) (2021) 4025–4036, https://doi.org/10.1093/eurheartj/ehab557. In press.