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FASTTRACK CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

Effects of lignocaine vs. opioids on antiplatelet activity of ticagrelor: the LOCAL trial

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Aims We assessed the impact of intravenous fentanyl and lignocaine on the pharmacokinetics and pharmacodynamics of ticagrelor in patients with unstable angina and non-ST-elevation myocardial infarction and their procedural analgesic efficacy and safety.

Methods and results Seventy patients undergoing coronary angiography with ticagrelor loading were included in the pharmacokinetic and pharmacodynamic analyses of this randomized trial. Plasma ticagrelor levels 2 h post-loading dose were significantly lower in the fentanyl arm than in the lignocaine treatment arm (598 vs. 1008 ng/mL, $P = 0.014$). The area under the plasma–time curves for ticagrelor (1228 vs. 2753 ng h/mL, $P < 0.001$) and its active metabolite (201 vs. 447 ng h/mL, $P = 0.001$) were both significantly lower in the fentanyl arm. Expression of activated platelet glycoprotein IIb/IIIa receptor (2829 vs. 1426 mean fluorescence intensity, $P = 0.006$) and P-selectin (439 vs. 211 mean fluorescence intensity, $P = 0.001$) was significantly higher at 60 min in the fentanyl arm. A higher proportion of patients had high on-treatment platelet reactivity in the fentanyl arm at 60 min using the Multiplate Analyzer (41% vs. 9%, $P = 0.002$) and 120 min using the VerifyNow (30% vs. 3%, $P = 0.003$) and VASP (37% vs. 6%, $P = 0.002$) assays. Both drugs were well tolerated with a high level of patient satisfaction.

Conclusions Unlike fentanyl, lignocaine does not impair the bioavailability or delay the antiplatelet effect of ticagrelor. Both drugs were well tolerated and effective with a high level of patient satisfaction for procedural analgesia. Routine procedural analgesia during percutaneous coronary intervention should be reconsidered and if performed, lignocaine is a beneficial alternative to fentanyl.

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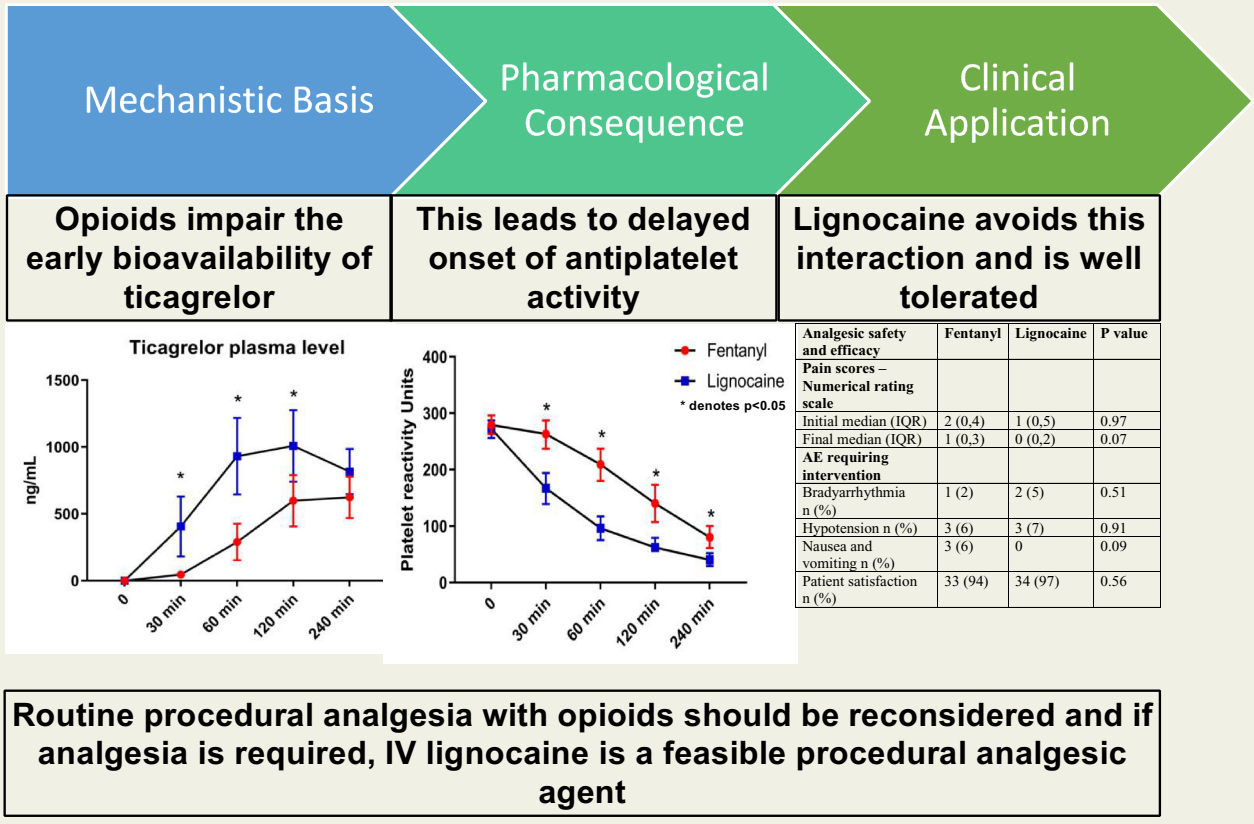
Graphical Abstract



Analgesic safety and efficacy	Fentanyl	Lignocaine	P value
Pain scores – Numerical rating scale			
Initial median (IQR)	2 (0,4)	1 (0,5)	0.97
Final median (IQR)	1 (0,3)	0 (0,2)	0.07
AE requiring intervention			
Bradyarrhythmia n (%)	1 (2)	2 (5)	0.51
Hypotension n (%)	3 (6)	3 (7)	0.91
Nausea and vomiting n (%)	3 (6)	0	0.09
Patient satisfaction n (%)	33 (94)	34 (97)	0.56

Keywords Opioid-P2Y$_{12}$ inhibitor interaction • Acute coronary syndromes • Oral P2Y$_{12}$ inhibitor treatment failure • Platelet reactivity • Pharmacokinetics • Analgesia

Introduction

Opioids remain the analgesic agent of choice in managing myocardial ischaemic pain. However, retrospective studies have raised concerns regarding potential interactions between opioids and oral P2Y$_{12}$ inhibitors, which are a cornerstone of therapy in myocardial infarction.[1–7] One of the proposed mechanisms is opioid-induced gastroparesis leading to impaired gastrointestinal absorption of oral P2Y$_{12}$ inhibitors.[8] Biochemical studies have demonstrated that opioids reduce the bioavailability and antiplatelet activity of all oral P2Y$_{12}$ inhibitors.[9–11] Due to the pharmacological interaction and the potential clinical implications of early oral P2Y$_{12}$ inhibitor treatment failure, the search for alternative analgesic agents to opioids has attracted major interest.

Intravenous (IV) lignocaine has been shown to be effective for ischaemic limb pain, has a rapid onset of action, short half-life, potential gastrointestinal prokinetic properties, and is generally well tolerated, including in patients with coronary artery disease.[12–14]

The aim of this study was to compare the effects of lignocaine vs. fentanyl on the bioavailability of ticagrelor and its antiplatelet effects in patients undergoing coronary angiography and percutaneous coronary intervention (PCI). Uniquely, it also sought to evaluate the safety and efficacy of lignocaine compared to fentanyl as procedural analgesia in patients presenting with unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI).

Methods

Study design and patient population

The LOCAL trial was a prospective, single-centre, double-blind, randomized, controlled trial conducted at The Alfred Hospital, Melbourne, Australia. Intravenous lignocaine was the experimental analgesic agent assessed in this trial compared to IV fentanyl, which is the standard of care in the cardiac catheterization laboratory at The Alfred Hospital and many institutions worldwide.

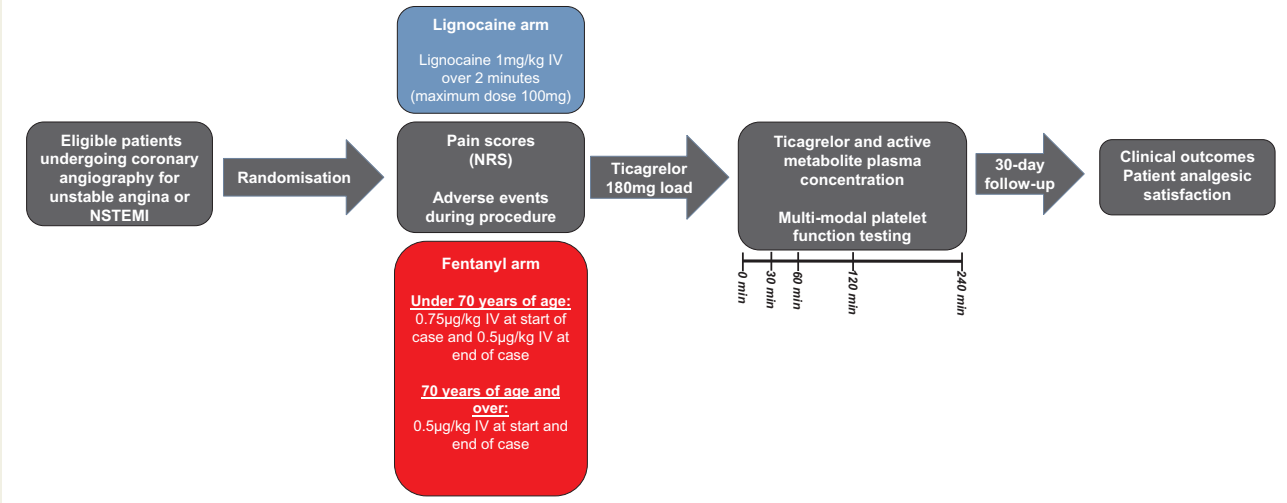


Figure 1 LOCAL study design. Trial design including inclusion/exclusion criteria, randomization and intervention details, safety and efficacy endpoints, pharmacokinetic and pharmacodynamic endpoints, and follow-up endpoints. IV, intravenous; NRS, numerical rating scale; NSTEMI, non-ST-elevation myocardial infarction.

Patients aged 18 years and over presenting with UA or NSTEMI undergoing coronary angiography were eligible for inclusion in the study. A diagnosis of UA or NSTEMI was based on documentation by the treating clinical team, review of cardiac biomarkers, and 12-lead electrocardiograms with compatible symptoms meeting American Heart Association/American College of Cardiology (AHA/ACC)-defined UA and NSTEMI criteria.[15] The exclusion criteria for the study included patients with any of the following: out-of-hospital cardiac arrest, ST-elevation myocardial infarction (STEMI), cardiogenic shock, morphine or opioid administration in the preceding 24 h or regular use, patients with a known coagulopathy or bleeding diathesis, allergy to fentanyl or lignocaine, bradycardia defined as heart rate <50 b.p.m. or evidence of atrioventricular block, ticagrelor, or other $P2Y_{12}$ inhibitor use in the preceding 10 days, or oral anticoagulation.

Randomization was performed in permuted blocks of 20 with an allocation ratio of 1:1 contained within sealed, opaque envelopes. The envelopes also contained instructions on dosing and administration of the drug. The envelopes were only opened by the treating cardiac catheterization laboratory staff once the coronary angiography case commenced. The envelopes with treatment allocation were discarded at the end of the case. The investigators responsible for blood sampling, ascertainment of pain scores, platelet function testing and pharmacokinetic analysis were blinded to treatment allocation. Participants were also blinded to treatment allocation.

The Alfred Hospital Human Research and Ethical Committee reviewed and approved the LOCAL study protocol (reference 258/19). The study was conducted in accordance with the principles of the Declaration of Helsinki (2000). All participants provided signed informed consent prior to the commencement of coronary angiography. The study protocol was registered prospectively on the Australian and New Zealand Clinical Trials Registry (ACTRN12619000648123). 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 corresponding author.

Study procedures

Participants were enrolled between February 2020 and December 2020 inclusive (see *Figure 1* for study design and intervention). Provision of IV midazolam as procedural sedation at the start of coronary angiography was at the discretion of the interventional cardiologist. Participants randomized to the fentanyl citrate (100 μg/2 mL, Hospira Australia) arm received 0.75 μg/kg of IV fentanyl at the start of the case if under 70 years of age, otherwise 0.5 μg/kg was given at the start of the case. If further analgesia was required during the case, IV fentanyl boluses were given at the discretion of the interventional cardiologist. Intravenous fentanyl 0.5 μg/kg was given at the end of the case.

Participants randomized to lignocaine hydrochloride (100 mg/5 mL—2%, Pfizer Australia) received 1 mg/kg (maximum dose of 100 mg) as a slow IV push over 2 min at the start of the case with a further 0.5 mg/kg given at the discretion of the cardiologist if further analgesia was required during the case. If satisfactory analgesia was not achieved after this, the patient crossed over to fentanyl. Otherwise, administration of opioid analgesia was avoided in this arm.

Patients with an indication for dual antiplatelet therapy and no contraindication were given 180 mg of ticagrelor orally as integral tablets with 250 mL of tap water at the end of the case. Patients who did not require dual antiplatelet therapy were included for the ascertainment of pain scores and safety only. If glycoprotein (GP) IIb/IIIa inhibitors were administered at the discretion of the interventional cardiologist, participants were included in the analysis; however, the antiplatelet effect of ticagrelor could only be assessed by the VASP assay, which is specific to $P2Y_{12}$ receptor inhibition and unaffected by downstream inhibition of the GPIIb/IIIa receptor.[16]

At the end of the case, participants were asked to rate their pain on the 11-point numerical rating scale (NRS) at the start of the case, worst pain during the case, end of the case, and at 2 h after the case. Investigators were also notified of any adverse events requiring intervention by the clinical cardiac catheterization staff.

Blood was sampled using an 18G IV cannula placed in the forearm. Blood was collected at baseline (time 0), 0.5, 1, 2, and 4 h after the

administration of ticagrelor with the first 5 mL of blood discarded to avoid spontaneous platelet activation.

Follow-up phone contact was made at 30 days post-study enrolment to ascertain the occurrence of major adverse cardiac events (MACE) defined as a composite endpoint of death, non-fatal myocardial infarction, target vessel revascularization, as well as patient satisfaction defined by whether patients were satisfied with the level of analgesia provided during their procedure and their willingness to receive the same analgesic agent for future procedures.

Pharmacokinetic assessment

Pharmacokinetic analysis was undertaken by investigators blinded to treatment allocation. Liquid chromatography tandem mass spectrometry was utilized to measure plasma concentrations of ticagrelor and its active metabolite AR-C124910XX at all sampling points using methodology adapted from Xu *et al.*[17] with modifications.

Samples were processed using protein precipitation method; in brief, 20 µL of each plasma sample was mixed with 10 µL of methanol, 40 µL of acetonitrile, and 10 µL of methanol containing ticagrelor internal standard (Ticagrelor d7, Cayman Chemical, Ann Arbor, MI, USA). Analysis was conducted on an Agilent 6495C in conjunction with an Agilent 1290 HPLC unit with a ZORBAX eclipse plus C18 column (2.1 mm × 100 mm 1.8 µm, Agilent). Solvent A comprised of water with 10 mM ammonium formate, whilst solvent B was 100% acetonitrile running at a flow rate of 0.5 mL/min. The following chromatography conditions were used: starting at 35% B, this was held for 0.5 min before ramping up to 65% B after 0.1 min. Over 1.2 min this was then linearly increased to 90% B, held at 90% for 0.5 min before ramping down to 35% B after a further 0.1 min. The column was equilibrated back to starting conditions over 1.1 min.

The following source conditions were used: gas temp, 150°C, gas flow rate 17 L/min, nebulizer at 20 psi, sheath gas temperature at 200°C, and sheath gas flow at 10 L/min. The instrument was operated in negative ionization mode running multiple reaction monitoring. The transitions used were: ticagrelor, 521.3/361.3 with a collision energy (CE) of 24 and Ticagrelor-d7, 528.3/368.3 with a CE of 24.

As we were unable to source a deuterated internal standard for AR-C12490XX, we monitored for the metabolite using two sets of transitions. The quantifier ion was 477.3/477.3 with a CE of 0, whereas the qualifier transition was 466.3/361.5 with a CE of 21. The quantifier ion was used to determine the concentration relative to the ticagrelor internal standard (quantifier ion measured as 528.3/528.3 with CE of 0) to obtain more accurate quantitation.

Pharmacodynamic assessment

Platelet function testing utilized the point of care assays VerifyNow (VFN; Accumetrics, San Diego, CA, USA) and Multiplate Analyzer (MPA; Roche Diagnostics International Ltd, Rotkreuz, Switzerland), flow cytometry including the VASP assay, assessment of P-selectin expression on the platelet surface, and GPIIb/IIIa activation. Except for the VASP assay, which was only utilized for the 2-h time point, all other assays were used to measure platelet function at all study time points. Whole blood was collected in citrate tubes for the pharmacodynamic analysis except for analysis using the MPA where hirudin tubes were used. The first 5 mL of blood was discarded to avoid spontaneous platelet activation.

The VFN point of care assay was used with the $P2Y_{12}$ cartridge to measure platelet reactivity (expressed as platelet reactivity units; PRU). The VFN is a point-of-care test conducted using whole blood analysed by recording light transmittance through blood samples in response to the platelet agonist adenosine diphosphate (ADP). The cartridges contain fibrinogen-coated beads to allow activated platelets within whole blood to agglutinate and increase light transmittance through the sample.

The MPA measures impedance through a sample of whole blood in response to ADP as a measure of platelet aggregation. Impedance through the sample measured by electrodes in sample wells rises with rising platelet aggregation. Briefly, diluted whole blood collected in hirudin tubes is added to sample wells with sample warmed to 37°C followed by addition of ADP as the agonist. Platelet aggregation was measured as the area under the impedance curve over a time period of 6 min (expressed as AUC).

For all flow cytometry assays, 10 000 platelets were gated after identification of platelets by side and forward scatter. All samples were processed through a BDFACS Fortessa X-20 cytometer (Firmware version 1.4 BD, Biosciences, San Jose, CA, USA) with events captured using BDFACS Diva software (Version 8.0.1, BD, Biosciences). Sample analysis was performed using FlowJo™ for Windows (version 10.7.1, BD, Ashland, OR, USA).

We used flow cytometry to assess P-selectin and the activation of GPIIb/IIIa with and without ADP stimulation. To achieve this, 50 µL of whole blood diluted in 2450 µL of phosphate-buffered saline was stimulated, or not, with 20 µM ADP (final concentration). Samples were simultaneously stained in the same tube with 10 µL anti-CD62P R-Phycoerythrin conjugated antibody (BD, clone AC 1.2) and 5 µL anti-activated GPIIb/IIIa (BD, clone PAC-1) for 15 min. Following this, samples were fixed with 1× Cell-Fix. Samples were then acquired on the flow cytometer.

Finally, we assessed platelet $P2Y_{12}$ receptor inhibition using the standardized VASP kit assay (Biocytex, Marseille, France) as previously described.[18] Briefly this is achieved by incubating whole blood with either prostaglandin E1 (PGE1) alone or in addition to ADP. Samples were fixed after which platelets were permeabilized and labelled with serine 239-phosphorylated VASP monoclonal antibody or an isotype control. Following this, samples were stained with fluorescein isothiocyanate-conjugated polyclonal goat-anti-mouse antibody. Platelet reactivity index (PRI) was expressed as a percentage by calculating geometric mean fluorescence index of phosphorylated VASP in samples treated with PGE1 alone compared to PGE1 + ADP.

High platelet reactivity was defined as PRI >50%, AUC >46 units, and PRU >208 as previously determined for the VASP, MPA, and VFN platelet function tests, respectively.[19]

Study outcomes

The pre-specified primary endpoint was plasma ticagrelor concentration at 2 h in the lignocaine compared to the fentanyl arm in an intention-to-treat analysis. The secondary study endpoints were (i) area under the ticagrelor plasma concentration-time curve between 0 and 4 h; (ii) platelet inhibition assessed by VFN, MPA, flow cytometry assays at all time points, and the VASP assay at the 2 h time point post-ticagrelor administration; (iii) percentage of patients with high on-treatment platelet reactivity (HTPR) at the above time points as previously defined;[19] (iv) pain NRS scores in both groups at the start and end of the case; (v) adverse effects in each group requiring intervention; and (vi) MACE recorded in each group at 30 days.

Statistical analysis

Sample size calculation was performed based on previous pharmacokinetic data demonstrating a 34% reduction in the plasma concentration of clopidogrel with concomitant morphine administration.[20] We calculated that 35 patients in each group would be required to identify a 20% reduction in ticagrelor plasma concentration to obtain a power of 80%, assuming a two-sided alpha of 0.05. Continuous variables were compared between both study arms with Student's *t*-test and Mann–Whitney *U*-test, depending on the presence or absence of normally distributed data

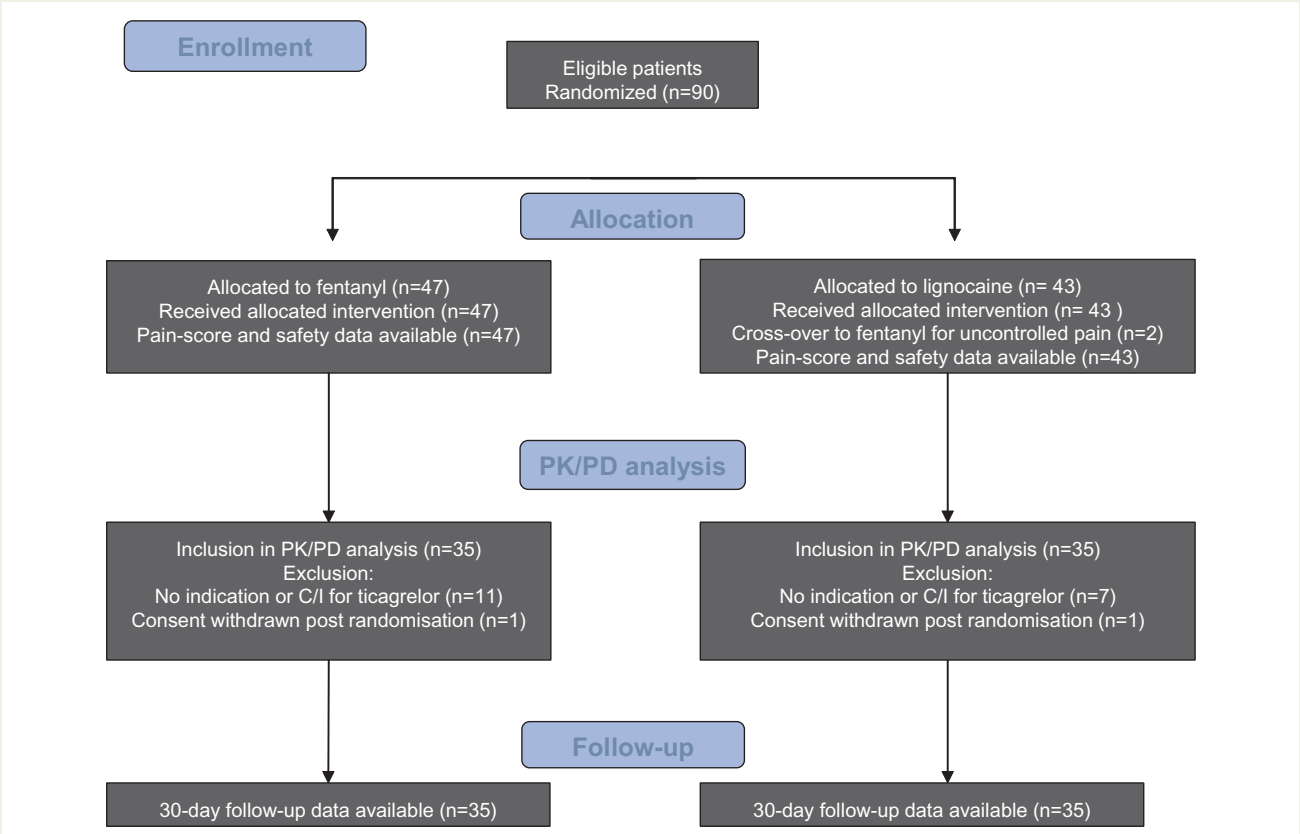


Figure 2 LOCAL study enrolment flow chart. Summary of patient enrolment, treatment allocation, endpoint analysis, and follow-up. C/I, contra-indication; PD, pharmacodynamic; PK, pharmacokinetic.

(as assessed by the Shapiro–Wilk test). Pharmacokinetic and pharmaco-dynamic data are presented as means and 95% confidence intervals or median values with interquartile range depending on the presence or absence of normally distributed data for each variable.

Comparisons between categorical variables were performed using Fisher's exact test. An intention-to-treat analysis was undertaken for all study endpoints. Two-sided *P*-values <0.05 were considered significant.

Results

Of 90 patients enrolled, 70 had an indication for dual antiplatelet therapy (*Figure 2*). All 90 patients were included in the analysis of analgesic efficacy and safety.

Platelet function testing and pharmacokinetic analysis were performed for the 70 patients who were administered ticagrelor loading at the end of the procedure with 35 patients in each arm. Baseline characteristics are presented in *Table 1* for the 70 patients included in the primary analysis and were not significantly different between the two arms. Complete pharmacokinetic data were obtained for all 70 patients. In terms of platelet function testing, complete data were obtained for the VASP assay in all 70 patients. For the remaining platelet function assays, complete data for 69 out of 70 patients were obtained except the P-selectin assay where complete data were available for 68 out of 70 patients.

Medication prescription in both arms was similar during the procedure (*Table 2*). All patients in the trial were treated with aspirin. Use of IV midazolam (fentanyl 37% vs. lignocaine 46%, $P = 0.47$) as routine procedural sedation and median unfractionated heparin (fentanyl 9000 IU vs. lignocaine 8000 IU, $P = 0.17$) doses for the procedure were similar between groups. The mean (standard deviation) total IV fentanyl dose was 99 (29) μg whilst the mean IV lignocaine dose was 85 (24) mg. Radial access was used predominately, with similar percentages in both study arms (fentanyl 91% vs. lignocaine 97%, $P = 0.3$). Of the patients administered ticagrelor, there was no difference in the proportion of patients treated with PCI between the two groups (fentanyl 63% vs. lignocaine 66%, $P = 0.8$).

Pharmacokinetic analysis

The primary endpoint, which was plasma ticagrelor levels 2 h post-ticagrelor load, was significantly lower in the fentanyl arm compared to the lignocaine arm (598 vs. 1008 ng/mL, $P = 0.014$; *Figure 3*). The area under the ticagrelor plasma–time curve in the first 4 h post-ticagrelor loading dose administration was also significantly lower in the fentanyl compared to lignocaine arm (1228 vs. 2753 ng h/mL,

Table 1 Baseline characteristics

	Fentanyl ($n = 35$)	Lignocaine ($n = 35$)	*P*-value
Age (years), mean ± SD	65 ± 11	67 ± 8	0.33
BMI (kg/m^2), median (IQR)	29 (27–34)	29 (26–33)	0.51
Male sex, *n* (%)	24 (69)	25 (71)	0.79
Current smoker, *n* (%)	9 (26)	5 (15)	0.23
HTN, *n* (%)	20 (57)	16 (46)	0.34
Diabetes mellitus on OHA/insulin, *n* (%)	7 (20)	4 (11)	0.32
Dyslipidaemia, *n* (%)	24 (69)	26 (74)	0.66
Heart failure, *n* (%)	3 (9)	1 (3)	0.30
Prior MI, *n* (%)	2 (6)	3 (9)	0.64
Prior PCI, *n* (%)	6 (17)	3 (9)	0.28
Previous CABG, *n* (%)	3 (9)	1 (3)	0.30
PVD, *n* (%)	1 (3)	0	0.31
CKD, *n* (%)	1 (3)	0	0.31
Cerebrovascular disease, *n* (%)	0	0	
Lung disease, *n* (%)	5 (14)	6 (17)	0.74
NSTEMI, *n* (%)	20 (57)	18 (51)	0.63
Radial access, *n* (%)	32 (91)	34 (97)	0.30
PCI, *n* (%)	22 (63)	23 (66)	0.8
TIMI 3 flow pre-PCI, *n* (%) ($n = 45$)	14 (64)	16 (70)	0.68
Obstructive CAD, *n* (%)	28 (80)	29 (83)	0.76
Haemoglobin (g/L), mean ± SD	137 ± 14	142 ± 16	0.14
Platelet count (10^9/L), mean ± SD	224 ± 61	244 ± 54	0.15
Creatinine (μmol/L), median (IQR)	75 (67–96)	75 (71–87)	0.91

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; HTN, hypertension; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; OHA, oral hypoglycaemic agents; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation; TIMI, Thrombolysis In Myocardial Infarction.

Table 2 Procedural medications

	Fentanyl ($n = 35$)	Lignocaine ($n = 35$)	*P*-value
Aspirin, *n* (%)	35 (100)	35 (100)	1
Midazolam, *n* (%)	13 (37)	16 (46)	0.47
Atropine, *n* (%)	1 (3)	2 (6)	0.56
Metaraminol, *n* (%)	3 (9)	2 (6)	0.64
GPIIb/IIIa inhibitor, *n* (%)	1 (3)	0	0.31
Adenosine, *n* (%)	4 (11)	4 (11)	1
Heparin (units)	9000 (5000–12 000)	8000 (5000–10 000)	0.17
Fentanyl dose (μg), mean ± SD	99 ± 29		
Lignocaine dose (mg), mean ± SD		85 ± 24	

GPIIb/IIIa, glycoprotein IIb/IIIa; SD, standard deviation.

$P < 0.001$). Ticagrelor plasma levels were significantly lower in the fentanyl arm at all time points except baseline and 240 min. With respect to the ticagrelor active metabolite AR-C12490XX, plasma levels were significantly lower in the fentanyl arm at all time points except at baseline (*Figure 3*). The area under the ticagrelor active metabolite plasma–time curve in the first 4 h post-ticagrelor loading was significantly lower in the fentanyl compared to lignocaine arm (201 vs. 447 ng h/mL, $P = 0.001$).

Pharmacodynamic assessment

Platelet reactivity results are provided in *Figure 4*. The VFN assay demonstrated significantly higher rates of platelet reactivity in the fentanyl arm at every time point after baseline.

Baseline platelet reactivity was lower in the fentanyl arm compared to the lignocaine arm based on the MPA. For the MPA as well as flow cytometry assessment of platelet surface P-selectin and activated GPIIb/IIIa expression, platelet reactivity was significantly higher at 30

and 60 min post-ticagrelor load in the fentanyl compared to lignocaine arm, but not at 120 or 240 min. The VASP assay, which was performed at 120 min post-ticagrelor load, demonstrated higher platelet reactivity in the fentanyl arm than in the lignocaine arm (40% fentanyl vs. 22% lignocaine PRU, $P = 0.001$).

High on-treatment platelet reactivity

Rates of HTPR based on consensus definitions as previously mentioned are provided in *Figure 5*. In the VFN assay, 59% in the fentanyl arm compared to 6% in the lignocaine arm met the definition of HTPR at 60 min ($P < 0.001$) remained significantly different at 120 min (30% fentanyl vs. 3% lignocaine, $P = 0.003$), but not at 240 min (6% fentanyl vs. 0% lignocaine, $P = 0.15$). In the MPA, rates of HTPR at 30 min (fentanyl 62% vs. lignocaine 29%, $P = 0.006$) and 60 min (fentanyl 41% vs. lignocaine 9%, $P = 0.002$) were significantly higher in the fentanyl arm but not at later time points. Thirty-seven percent of patients in the fentanyl arm and 6% in the lignocaine arm met the HTPR definition for the VASP assay at 120 min ($P = 0.002$).

Pain scores

Pain scores as reported by NRS were not significantly different at the beginning of the case between the fentanyl and lignocaine arms in the 90 patients enrolled in the study (2 vs. 1, $P = 0.97$; *Table 3*). Initial reported pain was predominately attributed to sheath insertion. Final pain scores, which were predominately related to sheath removal, were also not significantly different between the lignocaine and fentanyl arms (1 vs. 0, $P = 0.073$). There was no difference between maximal pain NRS scores and pain NRS score 2 h post-procedure. Ischaemic chest pain was experienced in two patients in the fentanyl arm and three patients in the lignocaine arm. Two patients in the lignocaine arm crossed over to fentanyl due to intolerable ischaemic chest pain during the procedure despite administration of two lignocaine doses.

Safety

Adjudicated safety events were similar in the two arms and are presented in *Table 3*. There was a trend towards greater nausea and vomiting requiring antiemetic therapy in the fentanyl arm (fentanyl 6% vs. lignocaine 0%, $P = 0.09$). There were no significant differences in rates of bradyarrhythmias (fentanyl 2% vs. lignocaine 5%, $P = 0.56$) or hypotension requiring intervention (fentanyl 6% vs. lignocaine 7%, $P = 0.64$) between groups. None of the patients developed sustained bradyarrhythmias, cardiogenic shock, or neurotoxicity.

Follow-up

Follow-up was complete in all patients administered ticagrelor in the study at 30 days. There were five patients in the fentanyl arm and six patients in the lignocaine arm with an unplanned readmission within 30 days (*Table 4*). Four patients in both groups were readmitted with non-cardiac complaints and subsequently discharged from the emergency department with negative troponin levels. One patient in the fentanyl arm re-presented to hospital with complete heart block 3 days post-PCI, which was not deemed to be related to the study intervention. One patient in the lignocaine arm was noted to have an acute reduction in haemoglobin at day 1 post-procedure, which was managed without requiring blood transfusion. One patient in the lignocaine arm had an out-of-hospital cardiac arrest 2 weeks after enrolment, which was considered to be unrelated to the study drug intervention. Overall patient satisfaction with procedural pain relief was 94% in the fentanyl arm and 97% in the lignocaine arm ($P = 0.56$).

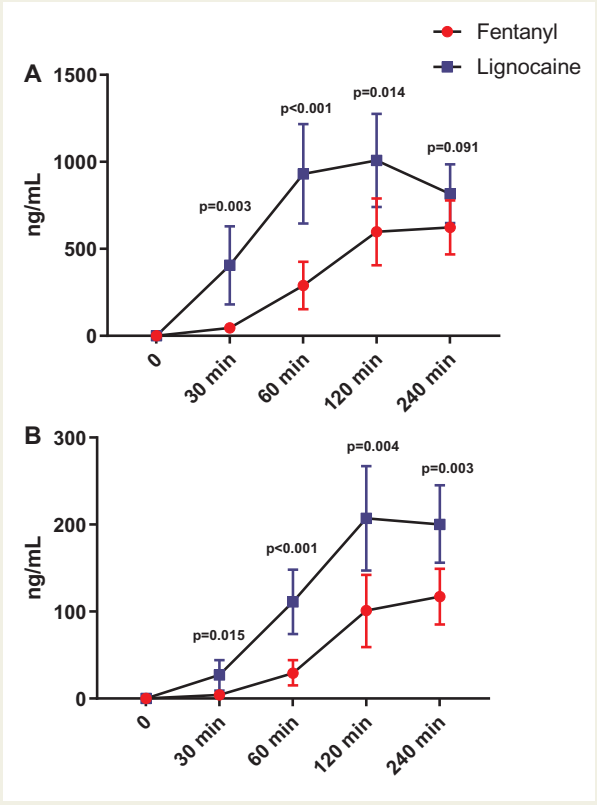


Figure 3 Bioavailability of ticagrelor and its active metabolite (AR-C124910XX) is impaired with fentanyl compared to lignocaine treatment. (*A*) Ticagrelor plasma concentrations in ng/mL at blood sampling time points to 4 h post-ticagrelor loading dose at time 0. Mean ticagrelor plasma levels with 95% confidence intervals presented in the fentanyl and lignocaine arms. (*B*) Ticagrelor active metabolite plasma concentrations in ng/mL at blood sampling time points to 4 h post-ticagrelor loading dose at time 0. Mean ticagrelor active metabolite plasma levels with 95% confidence intervals presented in the fentanyl and lignocaine arms. Student's *t*-test used, corresponding *P*-values presented above data points.

Discussion

This is the first study to our knowledge that tests IV lignocaine as an alternative analgesic agent for procedural analgesia in patients undergoing coronary angiography and PCI. Our study demonstrates that the use of IV lignocaine avoids the biochemical impact of IV fentanyl, which reduces early plasma ticagrelor levels and its early antiplatelet effect. We found comparable pain scores and that both drugs were well tolerated, with a high level of patient satisfaction in both groups (*Graphical abstract*).

Consistent with a study by Ibrahim *et al.*,[10] our study demonstrates that fentanyl interferes with the absorption and early antiplatelet effect of ticagrelor. This effect is consistent in the multi-modality

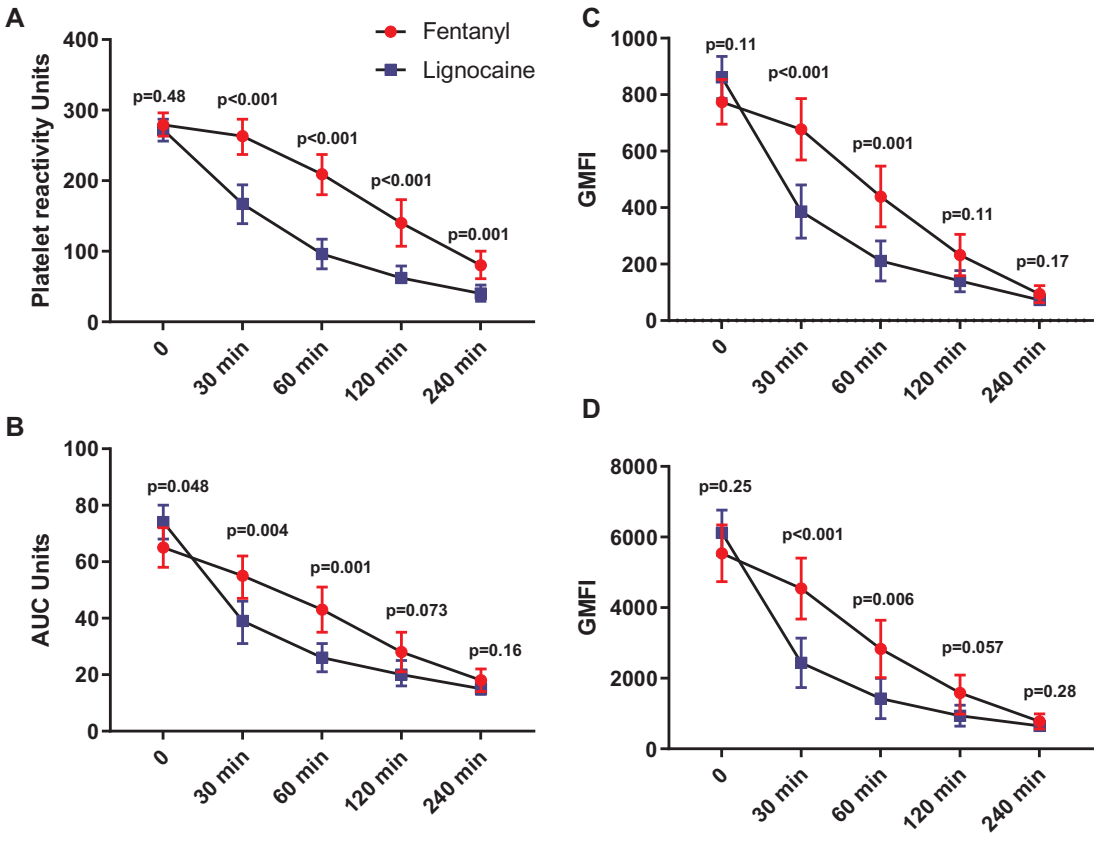


Figure 4 Platelet inhibition is delayed with fentanyl compared to lignocaine treatment. (*A*) Mean platelet reactivity units as assessed by the VerifyNow assay at blood sampling time points up to 4 h post-ticagrelor loading dose in the fentanyl and lignocaine treatment arms. Higher platelet reactivity unit levels represent greater platelet reactivity. (*B*) Area under the impedance curve units as determined with the Multiplate Analyzer assay. Higher area under the impedance curve levels represent greater platelet reactivity. (*C*) Mean geometric mean fluorescence intensity of P-selectin platelet surface expression in flow cytometry. Higher levels represent greater platelet reactivity. (*D*) Geometric mean fluorescence intensity of PAC-1 binding in flow cytometry reporting on the activation of glycoprotein IIb/IIIa. Higher levels of binding represent greater platelet reactivity. Data are presented as means and 95% confidence intervals. Student's *t*-test used, corresponding *P*-values presented above data points. AUC, area under the impedance curve; GMFI, geometric mean fluorescence intensity.

platelet function testing at the 30- and 60-min time points for all assays conducted. The VASP and VFN assays demonstrated a greater proportion of patients with HTPR at 2 h post-ticagrelor loading dose in the fentanyl arm.

Baseline platelet reactivity assessed by the MPA was significantly higher in the lignocaine arm than in the fentanyl arm; however, this finding was not replicated in any other assay. This most likely reflects inter-individual assay-related variability in platelet reactivity in the investigated patient population. A prior *ex vivo* study utilizing thromboelastography found evidence of impaired coagulation with incremental lignocaine concentrations added to whole human blood; however, these findings need to be reproduced.[21] The baseline platelet function results prior to ticagrelor loading in our study overall do not demonstrate any intrinsic antiplatelet effect of lignocaine when stimulated by ADP.

The delay in the gastrointestinal absorption of ticagrelor due to fentanyl in our patient population only affected the early antiplatelet response shortly after PCI. Previous trials have shown that therapeutic platelet inhibition is particularly delayed in patients with STEMI compared to more stable patients and that opioids further delay antiplatelet effects in the acute setting.[22–24] In a higher risk population, early treatment failure may be far more relevant. We previously identified a dose-dependent association between opioid dose and myocardial infarct size in a retrospective substudy analysis of the AVOID randomized controlled trial involving a STEMI population.[25] The clinical significance of this interaction, however, has been more challenging to elucidate, primarily as all published studies are retrospective in nature and the overall quality of the evidence is limited, with significant influence from confounding factors.[26] Ultimately, only prospective randomized controlled trials will be able to provide definitive answers on whether this biochemical interaction is clinically significant. However, in order for this to occur, a viable alternative analgesic agent is needed.

Fortunately, there are several promising agents available and an increasing interest to evaluate their suitability in treating ischaemic chest pain.[8] Lignocaine has been compared to a range of analgesic

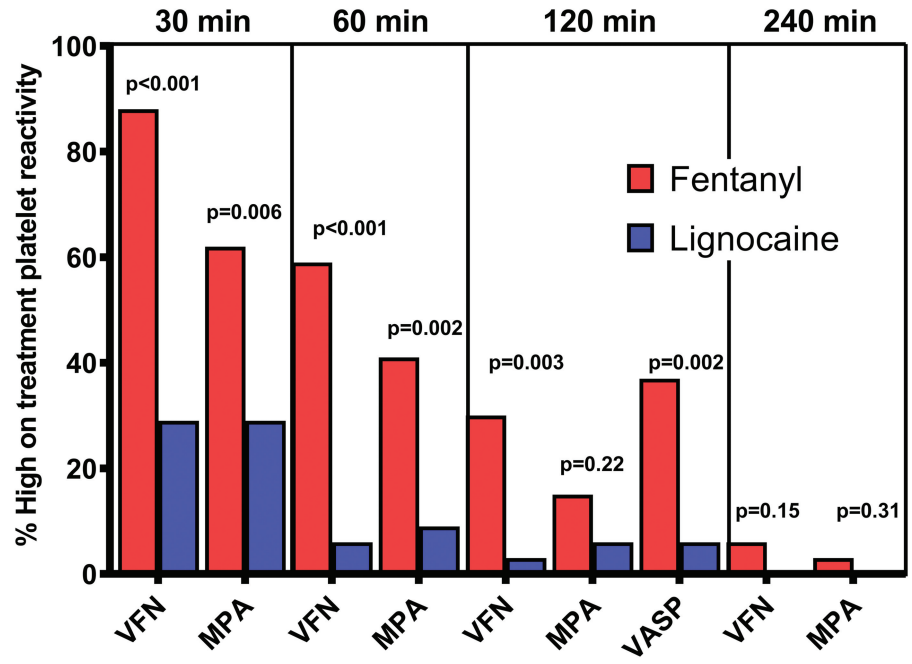


Figure 5 Proportions of high on-treatment platelet reactivity in the lignocaine and fentanyl arms. Proportion of patients meeting established high on-treatment platelet reactivity definitions for the VerifyNow, Multiplate Analyzer, and VASP assays stratified by blood sampling time points in the fentanyl and lignocaine arms. Fisher's exact test used, corresponding *P*-values between treatment arms presented above data points. MPA, Multiplate Analyzer; VASP assay; VFN, VerifyNow.

Table 3 Analgesic safety and efficacy

	Fentanyl ($n = 47$)	Lignocaine ($n = 43$)	*P*-value
Pain scores—numerical rating scale			
Initial, median (IQR)	2 (0–4)	1 (0–5)	0.97
Final, median (IQR)	1 (0–3)	0 (0–2)	0.07
Maximal pain score, median (IQR)	3 (1–5)	3 (0–6)	0.85
2 h post-procedure	0	0	0.33
AE requiring intervention, *n* (%)			
Bradyarrhythmia	1 (2)	2 (5)	0.51
Hypotension	3 (6)	3 (7)	0.91
Nausea and vomiting	3 (6)	0	0.09

AE, adverse events; IQR, interquartile range.

agents including morphine, ketorolac, chlorpromazine, and dihydroergotamine in randomized controlled trials for acute pain.[12] Lignocaine performed favourably to morphine in critical limb ischaemia and renal colic with significant reductions in pain and rapid onset of action within 15 min.[27,28] It is also well tolerated without significant hypotension or bradyarrhythmias at doses of 1–2 mg/kg.[13,29] In addition, a Cochrane review of lignocaine use as a prophylactic antiarrhythmic agent in STEMI was not associated with an increased risk of bradycardia, cardiogenic shock, or hypotension when compared to placebo.[14] This is consistent with our current study where lignocaine was well tolerated as procedural analgesia. In addition, a recent study demonstrated that IV acetaminophen resulted in a similar reduction in pain scores compared to opioids in the prehospital management of patients with suspected STEMI.[30]

Our present study demonstrated that pain scores in our stable population were relatively low and similar between patients receiving fentanyl and lignocaine when both agents were used as procedural analgesia. We chose a relatively stable, pain-free population to avoid the impact of recent opioid administration prior to coronary angiography (which formed part of the exclusion criteria), which may

Table 4 Thirty-day follow-up

	Fentanyl ($n = 35$), n (%)	Lignocaine ($n = 35$), n (%)	P-value
MACE	0	1 (3)	0.31
Cardiac arrest	0	1 (3)	0.31
Unplanned readmission	5 (14)	6 (17)	0.74
Non-cardiac readmission	4 (11)	4 (11)	1
Patient satisfaction	33 (94)	34 (97)	0.56

MACE, major adverse cardiac event (death, non-fatal myocardial infarction, and target vessel revascularization).

otherwise have influenced the pharmacokinetic analysis as the primary endpoint of the present study. As a result, most of the pain reported related to obtaining arterial access and sheath removal rather than ischaemic chest pain, which was experienced in only two patients in the fentanyl arm and three patients in the lignocaine arm.

Given the identified biochemical interaction and the relatively low pain scores during the procedure, we believe it is time to re-evaluate the role of opioids as routine procedural analgesia in stable patients undergoing coronary angiography, which is commonplace in Australia and North America.[31] Whilst we did not have a placebo arm to evaluate pain scores without any analgesia, the finding that most of the discomfort related to radial sheath insertion and removal suggests more liberal use of local anaesthetic may remove the need for routine premedication with opioid analgesia. In addition, IV lignocaine could be used to manage pain as required.

In terms of adverse events, lignocaine and fentanyl were well tolerated. We did not see an increased risk of bradyarrhythmias, tachyarrhythmias, or neurological toxicity at the doses of lignocaine used in the study. There was a trend towards higher rates of nausea and vomiting requiring antiemetic therapy in the fentanyl arm; however, this did not achieve statistical significance in contrast to previously reported studies.[32] There were no significant differences in clinical outcomes at follow-up in the two arms, although it has to be noted that this study was not powered to assess clinical endpoints and the sample size was relatively small. We will evaluate the safety of lignocaine at higher doses in our complementary prehospital trial in a population of patients with suspected STEMI.[33]

For the current study, we excluded unstable patients with STEMI, cardiogenic shock or out-of-hospital cardiac arrest. However, in these patients, morphine is often given at high doses. Given that our present study demonstrates that IV opioids, in contrast to lignocaine, impair bioavailability and antiplatelet effects of oral $P2Y_{12}$ inhibitors, a prospective randomized trial comparing lignocaine as an alternative to opioids in patients presenting with suspected STEMI has been initiated by us and is currently ongoing.[33] This trial will evaluate the efficacy of lignocaine for moderate-to-severe ischaemic chest pain (NRS ≥5/10) and also the safety of lignocaine in the prehospital setting in a suspected STEMI population. We hope that both trials will be complementary in providing valuable information regarding the utility of lignocaine as an alternative analgesic agent to opioids.

In addition to considering alternative non-opioid analgesic agents, other strategies to mitigate the opioid-oral $P2Y_{12}$ inhibitor interaction have been explored. These include utilizing metoclopramide as a prokinetic agent,[34] which appears promising, whilst IV methylnaltrexone as a peripheral opioid antagonist does not.[35,36] In addition, investigating the role of cangrelor, a highly potent IV $P2Y_{12}$ inhibitor[37,38] that bypasses the proposed mechanism of interaction and the upcoming novel subcutaneous $P2Y_{12}$ inhibitor selatogrel[39] will be important future directions of research.

Crushing or chewing ticagrelor has also been shown to lead to a faster rise in plasma ticagrelor levels and onset of antiplatelet activity;[40,41] however, opioids still appear to contribute to HPR in this setting as well.[42] In the ON-TIME 3 trial, where a loading dose of crushed ticagrelor was administered in the prehospital setting, ticagrelor plasma levels remained significantly lower in the fentanyl arm compared to IV paracetamol, suggesting that crushing alone does not completely mitigate the interaction with opioids.[30] Orodispersible ticagrelor on the other hand appears to be bioequivalent to integral ticagrelor, with the recent TASTER trial demonstrating equivalent platelet inhibition characteristics to the integral tablet.[43,44] For the present study, we decided to use integral ticagrelor tablets for all study participants given that this is the current standard practice in Australia, bioequivalence shown in the aforementioned TASTER trial, and to ensure consistency in the study population.

Limitations

There are several limitations of our study. The different platelet function assays employed in this study demonstrate different levels of variability in platelet reactivity. This inter-assay variability has been previously documented.[45,46] The baseline variability identified in the MPA assay with higher baseline platelet reactivity in the lignocaine arm is likely to reflect inter-individual variability as assessed by this test, given that no significant baseline differences were seen in any other assay. To avoid difficulties in interpretation based on assay-related variabilities, we chose a multi-modal platelet function testing approach.

Conclusions

Unlike fentanyl, IV lignocaine does not interfere with the bioavailability and antiplatelet effect of ticagrelor in patients presenting with UA and NSTEMI. When used as procedural analgesia in a relatively stable population, lignocaine was well tolerated and led to a high level of patient satisfaction with respect to procedural analgesic efficacy. Furthermore, the potential clinical implications of the early treatment delay of oral $P2Y_{12}$ inhibitors in the current study suggest that routine use of opioids in stable patients undergoing coronary angiography

and PCI should be avoided. Finally, our findings provide a strong justification to evaluate the safety and efficacy of non-opioid analgesia, such as lignocaine, to treat acute ischaemic chest pain, for example, in STEMI.

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Conflict of interest: none declared.

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Erratum

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Erratum to: CDR132L improves systolic and diastolic function in a large animal model of chronic heart failure

Sandor Batkai, Celina Genschel, Janika Viereck, Steffen Rump, Christian Bär, Tobias Borchert, Denise Traxler 4, Martin Riesenhuber, Andreas Spannbauer, Dominika Lukovic, Katrin Zlabinger, Ena Hasimbegovic, Johannes Winkler, Rita Garamvölgyi, Sonja Neitzel, Mariann Gyöngyösi, and Thomas *Thum Eur Heart J* 2021; doi:10.1093/eurheartj/ehaa791.

Upon issue publication, a supplementary file was inadvertently deleted which was present in the originally published version of this article available on Advance Access. This missing supplementary file has been reuploaded. The publisher apologizes for the error.