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Fast-track cardiac anaesthesia and early extubation pathway versus usual care for adults undergoing coronary artery bypass graft surgery: a two-centre pilot randomised controlled feasibility trial in Victoria, Australia

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ABSTRACT

Objectives To assess feasibility and preliminary clinical outcomes of a fast-track cardiac anaesthesia (FTCA) pathway for scheduled coronary artery bypass grafting (CABG).

Design Two-centre, open-label, blinded-endpoint, pilot randomised controlled trial.

Setting One public and one private hospital in Victoria, Australia.

Participants Adults undergoing scheduled isolated CABG with cardiopulmonary bypass, preserved left ventricular systolic function and low-to-moderate operative risk.

Interventions Participants were randomised 1:1 to usual care or an FTCA pathway comprising methadone, dexmedetomidine, remifentanil, magnesium, lignocaine, sugammadex-based reversal and structured early extubation.

Primary and secondary outcome measures Feasibility comprised five prespecified criteria: recruitment capacity, consent, study drug administration, absence of administration errors and retention. The primary clinical endpoint was extubation within 4 hours of intensive care unit admission, with operating-room extubation assigned zero hours. Secondary outcomes included extubation time, opioid requirements, pain, length of stay and safety. Analyses used Fisher's exact, Wilcoxon rank-sum and Kaplan-Meier/Cox methods; efficacy comparisons were exploratory.

Results Of 374 patients screened, 102 were eligible and 100 were randomised. Four of the five feasibility criteria were met at both centres. Recruitment capacity was 1.28 eligible patients per week at Hospital A and 2.07 at Hospital B; only Hospital B exceeded the threshold of two. Consent was 98.0%, study drug administration 100% without errors, and dropout 0%. Early extubation occurred in 27/50 FTCA vs 3/50 usual-care participants (risk difference 0.48, 95% CI 0.31 to 0.62). Median extubation times were 3.9 versus 10.8 hours (location shift −5.0 hours, 95% CI −7.2 to −3.2). Opioid requirements in the first 24 hours and severe pain were lower with FTCA. Length of stay was not clearly reduced; uncommon harms could not be excluded.

Conclusions Pathway delivery and retention were achievable, but recruitment feasibility was not established at both centres. Preliminary clinical findings support a definitive trial with centre-specific recruitment planning.

Trial registration number ACTRN12625001245482.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The randomised design, concealed allocation, blinded endpoint assessment, complete follow-up and intention-to-treat analysis reduce several important sources of bias, although treating anaesthetists were necessarily unblinded and the success of blinding of intensive care clinicians was not formally assessed.
⇒ The intervention was evaluated across one public and one private hospital using a prespecified, protocolised pathway with explicit feasibility criteria.
⇒ The pilot sample was designed to assess feasibility and preliminary efficacy and was not powered to detect uncommon adverse events or definitive effects on resource use.
⇒ Eligibility was restricted to selected low-to-moderate-risk patients undergoing isolated CABG, which limits generalisability to higher-risk and more complex cardiac surgical populations.
⇒ Because the intervention was delivered as an integrated pathway, the independent effects of its pharmacological components and its structured extubation workflow cannot be determined, and the observed effects apply to the pathway as a whole.

INTRODUCTION

Coronary artery bypass grafting (CABG) remains a common major cardiac operation

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worldwide, with contemporary data showing substantial procedural volumes across North America, Europe and Asia.[1–3] Enhanced recovery pathways increasingly emphasise early extubation and timely intensive care unit (ICU) discharge after cardiac surgery.[4 5] Fast-track cardiac anaesthesia (FTCA) is intended to achieve tracheal extubation within the early postoperative period, typically within four postoperative hours, without compromising safety.[6–8] Although FTCA principles are widely accepted and incorporated into enhanced recovery after cardiac surgery (ERAS) pathways,[9–11] the optimal pharmacological strategy remains uncertain and practice varies substantially across institutions.

This uncertainty is clinically relevant. Persistent opioid use after cardiac surgery occurs in approximately 5%–10% of previously opioid-naïve patients and is associated with chronic pain, impaired recovery and opioid-related harm.[12–15] Therefore, an effective FTCA strategy should not only facilitate early extubation but also provide durable analgesia and reduce postoperative opioid exposure. Methadone is attractive in this setting because it provides prolonged multimodal analgesia through μ-opioid receptor agonism, N-methyl-D-aspartate receptor antagonism and serotonin–norepinephrine reuptake inhibition. In cardiac surgery, it has been associated with lower pain scores and reduced analgesic requirements.[16–21] Remifentanil, magnesium and lignocaine may add titratable intraoperative analgesia, anti-hyperalgesic effects and additional opioid-sparing benefit.[22–27] Dexmedetomidine may further support fast-track recovery by providing cooperative sedation, sympatholysis and opioid-sparing analgesia with minimal respiratory depression.[28–31] Several studies have reported associations between dexmedetomidine use and shorter time to tracheal extubation, reduced ICU length of stay (LOS) and possible protection against postoperative acute kidney injury (AKI),[32 33] although findings are not uniform.

While these agents have usually been studied individually, no randomised trial has evaluated a structured FTCA pathway combining methadone, dexmedetomidine, remifentanil, magnesium and lignocaine within a protocolised extubation strategy. Our previous retrospective cohort study in elective CABG patients suggested that this bundle was associated with earlier extubation, lower postoperative opioid use and shorter ICU LOS compared with usual care.[34] However, observational data are limited by confounding, selection bias and centre-level practice effects, and cannot determine whether the apparent benefit reflects the pharmacological bundle, the structured extubation workflow or both.

We therefore conducted a two-centre pilot randomised controlled trial comparing a protocolised FTCA pathway, in which the pharmacological bundle, sugammadex-based neuromuscular reversal and a structured early extubation workflow were delivered together, with usual care in adults undergoing scheduled CABG surgery. The research question was deliberately pragmatic and pathway-level: does implementation of the complete FTCA pathway result in earlier extubation than current usual care? The trial was not designed to isolate the independent contribution of the pharmacological bundle from that of the extubation workflow, and the treatment effect estimated is that of the pathway as a whole. The primary objective was to assess feasibility across centres and obtain preliminary estimates of efficacy and safety to inform a definitive trial. We hypothesised that the FTCA pathway would be feasible to deliver and associated with earlier extubation and lower early postoperative opioid use, with no evidence of increased harm in this selected CABG population.

METHODS

Clinical trial registration

The trial was conducted at two hospitals in Victoria, Australia, one public (Austin Health) and one private (Epworth Eastern Hospital), which share common cardiac anaesthesia recommendations and clinical staff across cardiac surgery, anaesthesia, cardiology and intensive care. Participants were enrolled from 15 November 2025 to 16 June 2026, with follow-up completed on 17 July 2026. The complete study protocol is available as online supplemental file 1 (Study protocol). The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12625001245482).

Study design and participants

Eligible participants were adults aged 18 years or older undergoing elective or urgent isolated CABG via sternotomy with cardiopulmonary bypass (CPB), with a left ventricular ejection fraction (LVEF) of 50% or greater and a European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) below 6%. Elective and urgent admissions were classified according to the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) definitions.[35] Throughout, 'scheduled' surgery denotes both elective and urgent (non-emergency) admissions.

Patients were excluded if they required emergency or salvage surgery, redo cardiac surgery or any procedure other than isolated CABG; had New York Heart Association functional class greater than III, impaired right ventricular function, a preoperative cardiac assist device in situ, pulmonary hypertension (mean pulmonary artery pressure of 40 mm Hg or greater), a history of seizure or stroke, a body mass index of 50 kg/m² or greater, or protocol-defined renal, hepatic or respiratory dysfunction; had an allergy to methadone or dexmedetomidine, or had either drug or a regional anaesthetic technique planned as part of usual care; or were scheduled for surgery after 18:00, because of local reluctance to undertake tracheal extubation at night. The complete eligibility criteria, including the ANZSCTS admission definitions and the thresholds used to define right ventricular, renal, hepatic and respiratory dysfunction, are provided

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in online supplemental file 1 and summarised in online supplemental file 2 (Supplementary methods).

Randomisation and masking

Participants were randomised in a 1:1 ratio using a single computer-generated allocation sequence applied across both centres. Randomisation was not stratified by centre because of the modest planned sample size and because the participating centres shared common anaesthetic protocols, clinical staff and perioperative care pathways. Allocation was concealed using sequentially numbered, opaque, sealed envelopes opened in the operating theatre immediately before induction of anaesthesia. Treating anaesthetists were necessarily aware of allocation because of the nature of the intervention. Cardiac surgeons, intensivists, nursing staff, data collectors, outcome assessors and the trial statistician remained blinded to treatment assignment, and treatment groups were numerically coded with masked variable labels until completion of the primary analyses.

Several measures were used to protect blinding of the intensive care clinicians responsible for extubation decisions: trial allocation was not recorded in the ICU admission documentation, the structured operating room-to-ICU handover followed the standard institutional format without stating trial allocation, and intensivists were not present in the operating theatre. However, the intraoperative anaesthetic record remained accessible within the electronic medical record, and clinicians who consulted it could potentially have inferred allocation from documented drug exposures, such as methadone or dexmedetomidine, or from an operating-room extubation attempt. The success of blinding among intensive care clinicians was not formally assessed, and we therefore cannot exclude performance bias in relation to the clinician-determined primary endpoint; this is acknowledged as a limitation.

Standard care for all patients

All patients underwent standard preoperative assessment and optimisation, followed institutional fasting guidelines and received conventional surgical management and standardised institutional CPB management. Intraoperative monitoring followed institutional practice for cardiac surgery and included processed electroencephalographic monitoring, commenced before induction and maintained within predefined target ranges (bispectral index 40–60 or patient state index 25–50). Vasoactive therapy, fluid administration and blood product transfusion were at the discretion of the anaesthetist within institutional protocols. Full details of routine monitoring and CPB management are provided in online supplemental file 2 (Supplementary methods).

Protocolised pharmacological bundle: fast-track group

Patients allocated to the fast-track group received a protocolised multimodal pharmacological bundle designed to support rapid emergence, sustained analgesia and early tracheal extubation after CABG surgery. At induction, intravenous methadone 0.1–0.2 mg/kg was administered with propofol, remifentanil, dexmedetomidine, magnesium, lignocaine and vecuronium/rocuronium-based neuromuscular blockade, with dosing and titration targets detailed in table 1. Anaesthesia was maintained with volatile agents and/or propofol guided by processed electroencephalography. At the end of surgery, neuromuscular blockade was reversed with sugammadex.

Usual care group

In the usual-care group, decisions regarding operating-room extubation or transfer to ICU while intubated were at the treating anaesthetist's discretion, without a mandated 4-hour target. There was no protocolised use of remifentanil, magnesium, lignocaine or dexmedetomidine infusions (table 1). Antiarrhythmic therapy at separation from CPB, including lignocaine or magnesium for intermittent atrial fibrillation or other arrhythmias, was administered at the discretion of the treating anaesthetist according to standard institutional practice, as it would be outside the trial.

Extubation management and analgesia

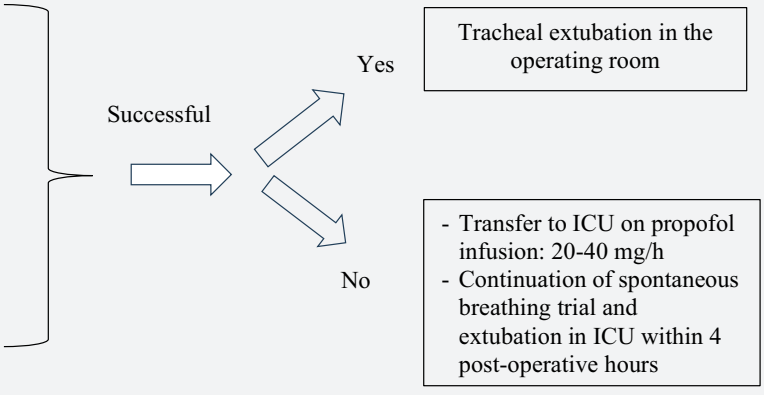
Decisions regarding operating-room extubation versus transfer to ICU intubated were at clinician discretion. In the ICU, extubation timing was determined by intensivists blinded to allocation, and an identical nurse-led weaning and extubation algorithm was applied to both treatment groups (online supplemental file 2, figure S1): extubation readiness was assessed on arrival in ICU and at least hourly thereafter in all participants, using the same prespecified criteria in both groups, namely haemodynamic stability, normothermia, acceptable chest drain output, adequate mentation, adequate analgesia, respiratory rate less than 20 breaths per minute and adequate gas exchange (arterial oxygen saturation greater than 92%, PaO_2/FiO_2 greater than 200 and $PaCO_2$ less than 55 mm Hg on pressure support of 5 cmH_2O with positive end-expiratory pressure of 5 cmH_2O and FiO_2 of 0.4 or less). Postoperative analgesia and sedation followed institutional standards in both groups (table 1).

Objectives and outcomes

The primary objective was to assess the feasibility and obtain preliminary estimates of efficacy and safety to inform a definitive trial. The primary clinical endpoint was successful early extubation, defined as removal of the tracheal tube within 4 hours of ICU admission. Time zero was the documented time of arrival in the ICU bed space, as recorded in the electronic medical record and reported to the ANZSCTS database; the endpoint was the documented time of tracheal tube removal. Participants extubated in the operating theatre before transfer were classified as achieving the primary clinical endpoint and assigned a ventilation time of 0 hours. Participants who were reintubated were classified according to the time of first extubation, with reintubation reported separately

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Table 1 Fast-track protocol and usual care

Usual care	Fast-track
Preoperative workup	
Routine preoperative cardiac workup and optimisation	
Preoperative medication	
► Discretion of treating anaesthetist	► Nil premedication
Preinduction anxiolysis/premedication	
► At discretion of treating anaesthetist. Methadone use not allowed	► Methadone: 0.1–0.2 mg/kg IV ► Bolus aliquots of propofol: 10–20 mg
Induction of anaesthesia	
► Any opioid (except for methadone) ► Any neuromuscular blocking agent	► Remifentanil: 1–2 mcg/kg ► Propofol: 10–50 mg ► Neuromuscular blocking agent: rocuronium: 1 mg/kg or vecuronium 0.1 mg/kg
Intraoperative	
► Any opioid (except for methadone) ► Volatile and/or propofol anaesthesia pre- and post CPB ► Depth of anaesthesia: Keep patient state index 25–50 or bispectral index 40–60	► Volatile or propofol anaesthesia pre CPB ► Propofol anaesthesia post CPB ► Remifentanil infusion: 0.1–0.3 µg/kg/min or target control infusion at 3–6 ng/mL ► Dexmedetomidine infusion: 0.5 µg/kg/hour ► Magnesium infusion: 15 mg/kg/hour ► Lignocaine infusion: 0.5 mg/kg/hour ► Rocuronium infusion: 0.5 mg/kg/hour ► Depth of anaesthesia: Keep patient state index 25–50 or bispectral index 40–60
Anaesthesia during CPB	
► Volatile and/or propofol anaesthesia at the discretion of treating anaesthetist	
Post CPB	
► Management at the discretion of treating anaesthetist	► Stop remifentanil during insertion of sternal wires
Skin closure	
Single pass oral gastric tube to decompress stomach	
Completion of surgery	
► Stop all anaesthesia agents ► Neuromuscular blockade reversal: at discretion of the anaesthetist ► Analgesia: at discretion of the anaesthetist	► Stop all anaesthesia agents ► Neuromuscular blockade reversal: sugammadex 4–8 mg/kg ► Analgesia: fentanyl 20–40 µg boluses (if indicated)
Initiate spontaneous breathing trial	
► Pressure support ventilation 5 cmH_2O ► PEEP: 5 cmH_2O ► Arterial saturation>92% ► $PaCO_2$<55 mm Hg ► FiO_2<0.4 ► PaO_2/FiO_2>200 ► Respiratory rate<20 b/min ► Adequate mentation ► Pain controlled ► Head lift off pillow ► Able to raise arms in air for 10s ► Stable haemodynamics ► Normothermia	
Postoperative analgesia	

Continued

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Table 1 Continued

Usual care	Fast-track
► Patient-controlled analgesia: PCA fentanyl 10 µg/bolus, 5 min boluses, 5 min lockout, no background infusion ► Paracetamol: 1 g every 6 hours for 48 hours ► Ketamine: 0.05–0.1 mg/kg/hour IV for refractory analgesia ► Tapentadol: 50–100 mg and oxycodone: 5–10 mg for oral analgesia once extubated ► Acute pain service review daily	
Postoperative agitation or delirium	
► Sedation/antipsychotics at the discretion of treating intensivist	

CPB, cardiopulmonary bypass; FiO2, fraction of inspired oxygen; PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen; PaO2/FiO2, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCA, Patient controlled analgesia; PEEP, Positive end-expiratory pressure.

(tables 2 and 3). This definition corresponds to the ANZSCTS Cardiac Surgery Database definition of postoperative ventilation time (ICU admission to ICU extubation) and does not include intraoperative ventilation or operating room-to-ICU transfer time.[35]

Key secondary efficacy outcomes were time to tracheal extubation over 48 hours, the proportion of patients extubated in the operating room or reintubated within 24 hours and cumulative opioid analgesia requirements at 24 hours and 48 hours, expressed as intravenous morphine equivalent dose.

Secondary service outcomes were ICU LOS, hospital LOS, ICU readmission, in-hospital mortality and 30-day mortality. Prespecified safety outcomes were bradycardia,

Table 2 Efficacy outcomes

		Treatment group			
Outcome	Overall n=100	Usual care n=50	FTCA n=50	Effect estimate (95% CI)	P value
Extubated within 4 hours of ICU admission	30 (30.0%)	3 (6.0%)	27 (54.0%)	0.48 (0.31 to 0.62)	<0.001*
Extubated in operating room	10 (10.0%)	0 (0.0%)	10 (20.0%)	0.20 (0.09 to 0.33)	0.001*
Postoperative ventilation time, ICU admission to tracheal extubation (hours)	8.6 (3.8, 12.1)	10.8 (7.2, 13.5)	3.9 (3.0, 9.8)	–5.0 (–7.2 to –3.2)	<0.001*
Postoperative rescue opioid use, 0–24 hours (mg IV morphine equivalent)	30.6 (22.0, 38.1)	33.7 (26.7, 40.0)	26.5 (20.0, 36.4)	–6.0 (–10.8 to –1.0)	0.018*
Postoperative rescue opioid use, 24–48 hours (mg IV morphine equivalent)	29.1 (20.0, 39.6)	32.7 (21.4, 41.0)	25.3 (19.2, 36.0)	–5.2 (–11.0 to 0.0)	0.059
Reintubation within 24 hours	1 (1.0%)	1 (2.0%)	0 (0.0%)	–0.02 (–0.10 to 0.05)	>0.999
Readmission to ICU from ward	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.00 (–0.07 to 0.07)	>0.999
Length of stay in ICU (hours)	69.1 (46.6, 95.3)	79.0 (59.0, 93.1)	58.2 (45.1, 96.5)	–13.9 (–25.0 to 2.9)	0.179
Length of stay in hospital (days)	7.9 (6.7, 9.6)	7.8 (6.7, 9.5)	7.9 (6.7, 9.6)	0.1 (–0.9 to 1.0)	0.791
Hospital mortality†	1 (1.0%)	1 (2.0%)	0 (0.0%)	–0.02 (–0.10 to 0.05)	>0.999
30-day mortality‡	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.00 (–0.07 to 0.07)	>0.999
Hospital re-presentations within 30 days of discharge	7 (7.0%)	4 (8.0%)	3 (6.0%)	–0.02 (–0.14 to 0.09)	>0.999

Data are presented as n (%) for binary outcomes and median (Q1, Q3) for continuous outcomes. Effect estimates are risk differences for binary outcomes and Hodges-Lehmann estimates of location shift for continuous outcomes, each with 95% CIs and calculated as fast-track minus control. P values were calculated using Fisher's exact test for binary outcomes and the Wilcoxon rank-sum test for continuous outcomes.
*p<0.05 was considered statistically significant.
†Hospital mortality was assessed up to hospital discharge. One patient died during the index hospitalisation on day 94 after randomisation. Accordingly, hospital mortality was 1, whereas 30-day mortality was 0 in both groups.
‡30-day mortality was defined as death from any cause within 30 days after randomisation.
FTCA, fast-track cardiac anaesthesia; ICU, intensive care unit.

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Table 3 Safety outcomes

Complication	Overall n=100	Treatment group			
		Usual care n=50	FTCA n=50	Effect estimates (95% CI)	P value
Cardiorespiratory					
Acute myocardial infarction	1 (1.0%)	1 (2.0%)	0 (0.0%)	−0.02 (−0.10 to 0.05)	>0.999
New-onset atrial fibrillation	36 (36.0%)	17 (34.0%)	19 (38.0%)	0.04 (−0.14 to 0.22)	0.835
Other arrhythmia	5 (5.0%)	3 (6.0%)	2 (4.0%)	−0.02 (−0.13 to 0.08)	>0.999
Permanent pacemaker	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.00 (−0.07 to 0.07)	>0.999
Bradycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.00 (−0.07 to 0.07)	>0.999
Hypotension	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.00 (−0.07 to 0.07)	>0.999
Pneumonia	3 (3.0%)	3 (6.0%)	0 (0.0%)	−0.06 (−0.16 to 0.02)	0.242
Pulmonary embolism	1 (1.0%)	1 (2.0%)	0 (0.0%)	−0.02 (−0.10 to 0.05)	>0.999
Reintubation within 24 hours	1 (1.0%)	1 (2.0%)	0 (0.0%)	−0.02 (−0.10 to 0.05)	>0.999
Other					
Return to theatre	6 (6.0%)	2 (4.0%)	4 (8.0%)	0.04 (−0.07 to 0.15)	0.678
Acute kidney injury	15 (15.0%)	5 (10.0%)	10 (20.0%)	0.10 (−0.04 to 0.24)	0.262
Deep vein thrombosis	2 (2.0%)	2 (4.0%)	0 (0.0%)	−0.04 (−0.13 to 0.04)	0.495
Cerebrovascular event	1 (1.0%)	0 (0.0%)	1 (2.0%)	0.02 (−0.05 to 0.10)	>0.999
Delirium	8 (8.0%)	6 (12.0%)	2 (4.0%)	−0.08 (−0.20 to 0.03)	0.269
Wound infection	1 (1.0%)	1 (2.0%)	0 (0.0%)	−0.02 (−0.10 to 0.05)	>0.999
Sepsis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.00 (−0.07 to 0.07)	>0.999
Bleeding-related					
Lowest haemoglobin (g/L)	86.0 (81.0, 92.0)	86.5 (82.0, 91.0)	85.0 (79.0, 92.0)	−1.00 (−4.00 to 3.00)	0.619
Drain output in 24 hours (mL)	775.0 (530.0, 1090.0)	790.0 (550.0, 1100.0)	755.0 (507.0, 1050.0)	−90.00 (−240.0 to 60.0)	0.257
Postoperative blood transfusion	63 (63.0%)	34 (68.0%)	29 (58.0%)	−0.10 (−0.28 to 0.09)	0.408
Opioid-related					
Severe pain (pain score≥7)	16 (16.8%)	13 (27.7%)	3 (6.3%)	−0.21 (−0.36 to −0.06)	0.006*
Respiratory depression	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.00 (−0.07 to 0.07)	>0.999
Deep sedation	3 (3.0%)	3 (6.0%)	0 (0.0%)	−0.06 (−0.16 to 0.02)	0.242
Antiemetic use	79 (79.0%)	38 (76.0%)	41 (82.0%)	0.06 (−0.10 to 0.22)	0.624
Naloxone use	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.00 (−0.07 to 0.07)	>0.999

Data are presented as n (%) for binary variables and median (Q1, Q3) for continuous variables. Effect estimates are risk differences for binary outcomes and Hodges-Lehmann estimates of location shift for continuous outcomes, each with 95% CIs and calculated as fast-track minus Control. P values were calculated using Fisher's exact test for binary outcomes and the Wilcoxon rank-sum test for continuous outcomes, as appropriate. *p<0.05 was considered statistically significant. Drain output at 24 hours was unavailable in one participant. Pain scores at 24 hours were not assessable in five participants (two FTCA and three usual care) as they remained mechanically ventilated at the assessment time point; the severe-pain analysis was therefore based on 48 FTCA and 47 usual-care participants.
FTCA, fast-track cardiac anaesthesia.

defined as heart rate less than 60 beats per minute; hypotension, defined as mean arterial pressure less than 65 mm Hg or systolic blood pressure less than 90 mm Hg; respiratory depression, defined as respiratory rate less than eight breaths per minute; deep sedation, defined as Richmond Agitation–Sedation Scale score of −4 or −5, or an equivalent local scale indicating unresponsiveness to voice and requiring repeated physical stimulation[36]; severe pain, defined as a numerical rating scale pain score of 7 or greater; and postoperative surgical complications. Haemodynamic and respiratory safety outcomes were ascertained by daily investigator review of the ICU and ward clinical records over the first 48 postoperative hours and were recorded as adverse events when the abnormality was sustained for at least 5 min despite first-line management or required escalation of therapy: for bradycardia, the administration of chronotropic therapy or institution of pacing; and for hypotension, escalation of vasoactive support beyond routine protocolised titration. Transient excursions below these numerical thresholds during routine titration of vasoactive infusions, which are near-universal after CPB, were not recorded as adverse events. Postoperative complications were classified using European Perioperative Clinical Outcome definitions.[37] Disability-free survival and quality of recovery scores were prespecified efficacy outcomes but were

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Table 4 Prespecified feasibility criteria and observed performance, by centre

Prespecified criterion	Threshold	Hospital A (Austin Health, public)	Hospital B (Epworth Eastern, private)	Overall	Criterion met (observed estimate)
Recruitment capacity	>2 eligible patients per centre per week	1.28 per week (39 patients; 95% CI 0.91 to 1.75)	2.07 per week (63 patients; 95% CI 1.59 to 2.65)	3.35 per week across both centres (102 patients; 95% CI 2.73 to 4.07)	Hospital A: No Hospital B: Yes
Consent rate	>40% of approached patients	100% (39/39; 95% CI 91.0 to 100)	96.8% (61/63; 95% CI 89.0 to 99.6)	98.0% (100/102; 95% CI 93.1 to 99.8)	Yes, at both centres
Successful study drug administration	>80% of FTCA participants receiving both methadone and dexmedetomidine as intended	100% (21/21; 95% CI 83.9 to 100)	100% (29/29; 95% CI 88.1 to 100)	100% (50/50; 95% CI 92.9 to 100)	Yes, at both centres
No drug administration errors	Zero errors in FTCA participants	0 errors (0/21 FTCA participants)	0 errors (0/29 FTCA participants)	0 errors (0/50 FTCA participants)	Yes, at both centres
Participant retention	<2% post-randomisation dropout	0% dropout (0/39; 95% CI 0.0 to 9.0)	0% dropout (0/61; 95% CI 0.0 to 5.9)	0% dropout (0/100; 95% CI 0.0 to 3.6)	Yes, at both centres
Randomisation rate (reported for context)	Not a prespecified criterion	1.28 per week (39 participants; 95% CI 0.91 to 1.75)	2.00 per week (61 participants; 95% CI 1.53 to 2.58)	3.29 per week across both centres (100 participants; 95% CI 2.67 to 4.00)	Not applicable

Rates were calculated using the unrounded elapsed recruitment period of 213 days (213/7 weeks) at each centre, from 15 November 2025 to 16 June 2026. The duration of 30.4 weeks is rounded for presentation. Weekly rates are reported with exact Poisson 95% CIs, and proportions with exact binomial (Clopper-Pearson) 95% CIs. Recruitment capacity was calculated from the 102 patients remaining after detailed eligibility assessment and proceeding to consent, not from the 160 patients who met initial screening criteria. Overall weekly rates represent the combined yield across both centres and are not rates per centre. Consent rates use all patients approached as the denominator. No drug administration errors were recorded at either centre. Criterion met indicates whether the observed point estimate satisfied the stated threshold. CIs describe precision and were not used as additional pass/fail thresholds; in particular, the observed absence of dropout does not exclude an underlying dropout rate of 2% or higher.
Hospital A is Austin Health, a university-affiliated public teaching hospital. Hospital B is Epworth Eastern Hospital, a private hospital.
FTCA, fast-track cardiac anaesthesia.

not assessed because funding for the research nursing support required for structured disability follow-up was unavailable.

Five feasibility criteria were prespecified in the protocol: recruitment capacity (more than two eligible patients per centre per week); consent rate (more than 40% of approached patients); successful study drug administration (methadone and dexmedetomidine administered as intended in more than 80% of FTCA participants); no drug administration errors; and participant retention (less than 2% post-randomisation dropout). For time-to-event analyses, patients who died before extubation or remained intubated beyond 48 hours were censored at death or at 48 hours, respectively.

Data collection

Data were extracted prospectively from electronic medical records into a secure, password-protected, de-identified database and comprised the preoperative, intraoperative and postoperative variables reported in table 4 and online supplemental file 2. Intraoperative methadone and other opioid doses were recorded separately from non-opioid adjuncts, and postoperative opioid consumption was expressed as intravenous morphine equivalents. Estimated glomerular filtration rate (eGFR) was calculated centrally for all participants from isotope dilution mass spectrometry-traceable serum creatinine using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation without a race coefficient, because the two centres use different eGFR reporting conventions.[38 39] Data on race and ethnicity were not collected because these variables are not routinely recorded in the participating hospitals' cardiac surgical databases.

Sample size calculation

The planned sample size was 100 participants (50 per group), chosen pragmatically to provide reasonable precision around feasibility estimates while being sufficient to

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detect a clinically informative signal for the primary clinical endpoint, extubation within 4 hours of ICU admission. Based on institutional audit data and published fast-track extubation studies, early extubation was assumed to occur in 10% of usual-care and 36% of FTCA patients; 48 patients per group were required to detect this absolute increase of 26 percentage points with 80% power and a two-sided α of 0.05 (normal-approximation test for two independent proportions with continuity correction), and the target was increased to 50 per group to allow for dropouts or postoperative exclusions. The sample was also adequate for the key continuous secondary outcome, time to tracheal extubation: prior institutional data (mean (SD) 4.13 (5.95) hours with fast-track care versus 8.60 (8.20) hours with usual care in patients with EuroSCORE II below 6%; common SD 7.1 hours) indicated that 40 patients per group would detect a difference of 4.47 hours with the same power and α. These supporting calculations do not alter the feasibility framework of the study, and all efficacy comparisons are interpreted as preliminary and hypothesis-generating.

Patient and public involvement

Patients and members of the public were not involved in the design, conduct, reporting or dissemination planning of this pilot trial.

Statistical analysis

All primary analyses followed the intention-to-treat principle, including all randomised patients in the groups to which they were assigned, regardless of protocol deviations. The safety analysis set comprised all randomised patients who received their allocated perioperative management, which in practice included all 100 participants. There were no missing primary endpoint data. Missingness was low (≤5%) for secondary and safety outcomes and baseline descriptive variables (body mass index 2, cross-clamp time 1, drain output 1, 24-hours pain score 5), and no imputation was undertaken.

Baseline characteristics were summarised as counts (percentages) for categorical variables and mean (SD) or median (IQR) for continuous variables, as appropriate. Because several key outcomes, including time to extubation and lengths of stay, were markedly right-skewed on inspection of histograms, quantile-quantile plots and the Shapiro-Wilk test, non-parametric descriptors and rank-based methods were prespecified and applied uniformly to continuous outcomes. For binary outcomes, including the primary clinical endpoint, effect estimates were expressed as risk differences with 95% CIs, calculated using Newcombe score methods, and compared using Fisher's exact tests. For continuous outcomes, effect estimates were expressed as Hodges-Lehmann estimates of location shift with 95% CIs and compared using the Wilcoxon rank-sum test.

Time-to-event analyses for time to extubation were restricted to the first 48 hours after ICU admission and used Kaplan-Meier curves, with groups compared using the log-rank test. Patients extubated in the operating room were assigned an extubation time of zero hours in the primary time-to-event analysis, because on-table extubation was a prespecified component of the FTCA pathway. Exploratory Cox proportional hazards models were used to estimate unadjusted HRs and HRs adjusted for admission status (elective vs urgent) and EuroSCORE II, with 95% CIs.

As a sensitivity analysis, the Kaplan-Meier and Cox analyses were repeated after excluding patients extubated in the operating room, restricting the analysis to patients who arrived in ICU intubated. Because operating-room extubation is a post-randomisation event that is itself influenced by the allocated intervention, this analysis does not preserve the causal comparison afforded by randomisation and is presented as a descriptive assessment of robustness only. A per-protocol sensitivity analysis was prespecified in the event of protocol deviations. Because all randomised participants received their allocated perioperative management, with no study drug violations, crossovers or missing primary endpoint data, the per-protocol population was identical to the intention-to-treat population.

Feasibility proportions were summarised with exact binomial (Clopper-Pearson) 95% CIs. Recruitment capacity was calculated using patients who remained eligible after detailed assessment, rather than those who met initial screening criteria. Recruitment, screening and randomisation rates were calculated as counts per week of centre recruitment time, using the unrounded common recruitment period of 213 days (213/7 weeks) at each centre, and reported with exact Poisson 95% CIs; overall weekly rates describe the combined number of patients across both centres and are not rates per centre. Feasibility criteria were assessed by comparing the observed point estimates with the stated thresholds; CIs describe precision and were not additional pass/fail criteria. All p values were two-sided, and a p value less than 0.05 was considered statistically significant for the primary clinical endpoint. No adjustment was made for multiplicity; secondary, safety and post hoc outcomes are interpreted as exploratory, and statistically significant efficacy findings are regarded as preliminary signals to inform a definitive trial. All analyses were performed using R V.4.4.1 (R Core Team; R Foundation for Statistical Computing, Vienna, Austria).[40]

RESULTS

Participant flow and feasibility

Between 15 November 2025 and 16 June 2026, a recruitment period of 30.4 weeks, 374 patients scheduled for cardiac surgery were screened for eligibility, 253 at Hospital A and 121 at Hospital B. Of these, 160 met initial screening criteria, 80 at each centre. 58 patients were subsequently excluded at detailed assessment because they met one or more protocol-defined exclusion criteria, 41 at Hospital A and 17 at Hospital B. The remaining 102

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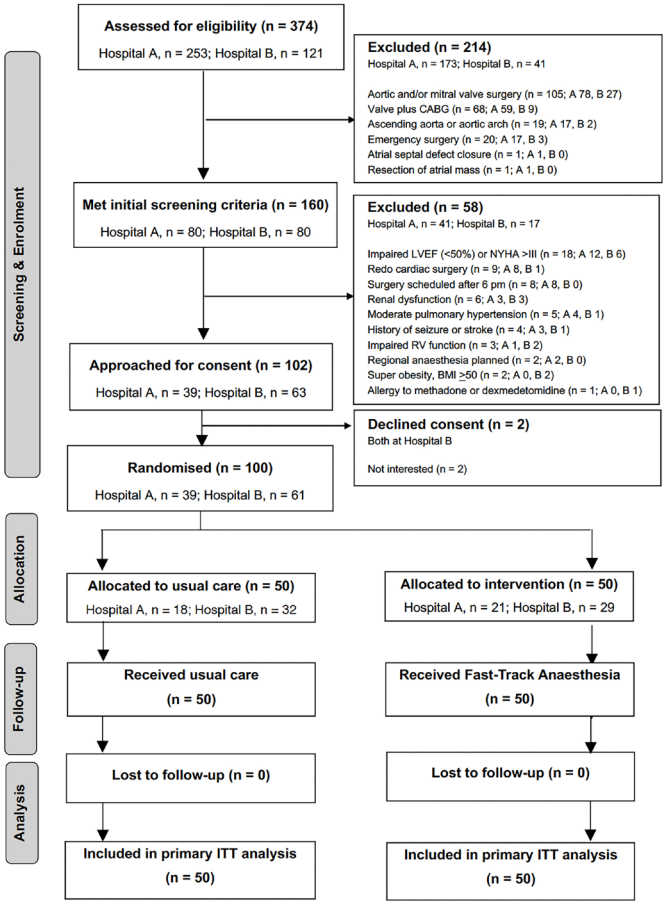


Figure 1 CONSORT flow diagram. Participant screening, consent, randomisation, allocation, follow-up and analysis. The 214 patients excluded at initial screening did not meet the inclusion criterion of primary isolated CABG (valve surgery with or without CABG, surgery on the ascending aorta or arch, and other procedures) or required emergency surgery; their distribution by reason and centre is shown in the figure. BMI, body mass index; CABG, coronary artery bypass grafting; CONSORT, Consolidated Standards of Reporting Trials; ITT, intention to treat; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricular.

patients were eligible and were approached for consent, 39 at Hospital A and 63 at Hospital B. Two patients declined consent, both at Hospital B. 100 patients provided written informed consent and were randomised, 50 to the FTCA pathway and 50 to usual care (figure 1). Hospital A randomised 39 participants and Hospital B randomised 61. All randomised participants received the allocated perioperative management. Follow-up was completed on 17 July 2026, no participants were lost to follow-up, and primary clinical endpoint data were available for all 100 participants.

Four of the five prespecified feasibility criteria were met at both centres: consent rate, successful study drug administration, absence of drug administration errors and participant retention (table 4). Recruitment capacity, calculated using the number of patients remaining eligible after detailed assessment, was 1.28 patients per week at Hospital A (39 patients; 95% CI 0.91 to 1.75) and 2.07 patients per week at Hospital B (63 patients; 95% CI 1.59 to 2.65). The combined rate across both centres was 3.35 eligible patients per week (102 patients; 95% CI 2.73 to 4.07). The prespecified threshold of more than two eligible patients per centre per week was therefore met at Hospital B but not at Hospital A, based on the observed rates. The CI for Hospital B included values below the threshold.

Screening rates were 8.31 patients per week at Hospital A (95% CI 7.32 to 9.40) and 3.98 per week at Hospital B (95% CI 3.30 to 4.75). At each centre, 80 patients met initial screening criteria, corresponding to 2.63 patients per week (95% CI 2.08 to 3.27). These patients represented 31.6% of those screened at Hospital A (80/253; 95% CI 25.9 to 37.7) and 66.1% at Hospital B (80/121; 95% CI 57.0 to 74.5). Overall, 58 of these 160 patients were subsequently excluded at detailed assessment (36.3%; 95% CI 28.8 to 44.2). Exclusions were more frequent at Hospital A (41/80; 51.3%; 95% CI 39.8 to 62.6) than at Hospital B (17/80; 21.3%; 95% CI 12.9 to 31.8).

The most frequent reasons for exclusion were impaired left ventricular function or New York Heart Association class greater than III (n=18), redo cardiac surgery (n=9) and surgery scheduled to commence after 18:00 (n=8). Reasons for exclusion by centre are reported in online supplemental file 2, table S1. No patient was withheld from approach because of staffing, research personnel availability, workflow constraints or clinician preference regarding the trial interventions. Consent rates among all patients approached were 100% at Hospital A (39/39; 95% CI 91.0 to 100), 96.8% at Hospital B (61/63; 95% CI 89.0 to 99.6) and 98.0% overall (100/102; 95% CI 93.1 to 99.8). Both centres exceeded the prespecified consent threshold of more than 40% of approached patients.

Randomisation rates were 1.28 participants per week at Hospital A (95% CI 0.91 to 1.75), 2.00 per week at Hospital B (95% CI 1.53 to 2.58) and 3.29 per week across both centres (95% CI 2.67 to 4.00). All 50 FTCA participants received both methadone and dexmedetomidine as intended (21 at Hospital A and 29 at Hospital B; 100%, 95% CI 92.9 to 100), with no drug administration errors or protocol-defined study drug violations at either centre, so the study drug administration and drug administration error criteria were met at both centres. No usual care participant received methadone, dexmedetomidine or remifentanil. 12 usual care participants received a lignocaine infusion and four received magnesium, in each case administered at separation from CPB as routine management of intermittent atrial fibrillation or other arrhythmias; such use was permitted within usual care by the protocol and did not constitute a protocol deviation (online supplemental file 2, table S2). No post-randomisation dropouts were recorded (0/100; 0%; 95% CI 0.0 to 3.6), meeting the retention threshold on the basis of the observed dropout rate.

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Table 5 Baseline characteristics of the trial population

Characteristic	Overall n=100	Usual care n=50	FTCA n=50
Hospital A (participants)	39 (39.0%)	18 (36.0%)	21 (42.0%)
Hospital B (participants)	61 (61.0%)	32 (64.0%)	29 (58.0%)
Age (years)	70.0 (64.0, 78.5)	72.0 (64.0, 78.0)	69.5 (65.0, 79.0)
Male	87 (87.0%)	42 (84.0%)	45 (90.0%)
BMI (kg/m²)	27.9 (25.2, 31.5)	28.0 (25.1, 32.9)	27.9 (25.3, 31.4)
Current smoker	22 (22.0%)	12 (24.0%)	10 (20.0%)
Elective surgery	57 (57.0%)	27 (54.0%)	30 (60.0%)
Hypertension	76 (76.0%)	37 (74.0%)	39 (78.0%)
Prior TIA with no deficit	7 (7.0%)	4 (8.0%)	3 (6.0%)
Diabetes mellitus	28 (28.0%)	16 (32.0%)	12 (24.0%)
COPD	5 (5.0%)	2 (4.0%)	3 (6.0%)
EuroSCORE II	1.26 (0.8, 1.7)	1.3 (0.8, 1.8)	1.1 (0.9, 1.5)
LVEF (%)	57.0 (51.0, 62.5)	55.5 (50.0, 60.0)	59.5 (53.0, 65.0)
Haemoglobin (g/L)	139.5 (128.5, 149.0)	139.0 (129.0, 150.0)	140.0 (128.0, 149.0)
Platelet count (×10^9 /L)	228.5 (186.0, 276.0)	223.5 (181.0, 248.0)	240.5 (188.0, 300.0)
White cell count (×10^9 /L)	7.3 (6.1, 8.4)	7.7 (6.2, 8.5)	7.1 (5.9, 8.0)
PT (s)	12.0 (11.4, 13.0)	12.0 (11.0, 13.0)	12.0 (11.7, 13.0)
aPTT (s)	26.5 (24.0, 29.0)	26.0 (24.0, 31.0)	27.0 (24.0, 29.0)
INR	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)
Creatinine (µmol/L)	86.0 (73.0, 106.0)	82.5 (70.0, 106.0)	88.5 (81.0, 106.0)
eGFR (mL/min/1.73 m²)	75.9 (57.9, 88.4)	79.5 (57.0, 89.3)	75.2 (58.2, 86.0)

Data are n (%) for categorical variables and median (Q1, Q3) for continuous variables, as appropriate. BMI was unavailable in two participants; summaries were calculated using available data.
aPTT, activated partial thromboplastin time; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; FTCA, fast-track cardiac anaesthesia; INR, international normalised ratio; LVEF, left ventricular ejection fraction; PT, prothrombin time; TIA, transient ischaemic attack.

Baseline and intraoperative characteristics

Baseline characteristics were broadly similar between groups (table 5). The median age was 70.0 years, and 87.0% of patients were male, the median EuroSCORE II was 1.26, and the median LVEF was 57.0%. Most patients were admitted for elective surgery, and major comorbidities were balanced between groups.

Intraoperative characteristics and drug exposure are summarised in online supplemental file 2, table S2. CPB duration, aortic cross-clamp time, vasoactive support and pump blood use were similar between groups. Intraoperative opioid and adjunct use differed according to treatment allocation. In the FTCA group, the median methadone dose was 20.0 mg and all patients received intraoperative dexmedetomidine; usual care patients received standard institutional opioid regimens without a protocolised methadone–dexmedetomidine pathway.

Efficacy outcomes: extubation outcomes

Extubation within 4 hours of ICU admission occurred in 27 (54.0%) FTCA patients and 3 (6.0%) usual-care patients (risk difference 0.48, 95% CI 0.31 to 0.62; p<0.001). Operating-room extubation occurred in 10 (20.0%) FTCA patients and no usual-care patients (risk difference 0.20, 95% CI 0.09 to 0.33; p=0.001). Time to extubation was shorter in the FTCA group, with a Hodges-Lehmann location shift of −5.0 hours (95% CI −7.2 to −3.2; p<0.001). Total duration of mechanical ventilation showed a similar direction of effect (table 2).

In time-to-event analysis, the cumulative proportion of patients extubated over time was higher in the FTCA group (figure 2; log-rank p=0.002). The unadjusted HR for extubation was 1.85 (95% CI 1.25 to 2.76), and the adjusted HR was 1.88 (95% CI 1.26 to 2.82). Reintubation within 24 hours was uncommon and did not differ significantly between groups. In the sensitivity analysis excluding operating-room extubation, 90 patients remained: 50 usual care patients and 40 FTCA patients. Median time to extubation remained shorter with FTCA, 6.1 versus 10.8 hours, and the cumulative proportion extubated remained higher (log-rank p=0.034; online supplemental file 2, figure S2). The unadjusted and adjusted HRs were 1.56 (95% CI 1.02 to 2.38) and 1.54 (95% CI 1.00 to 2.36), respectively. Because this sensitivity analysis conditions on a post-randomisation event,

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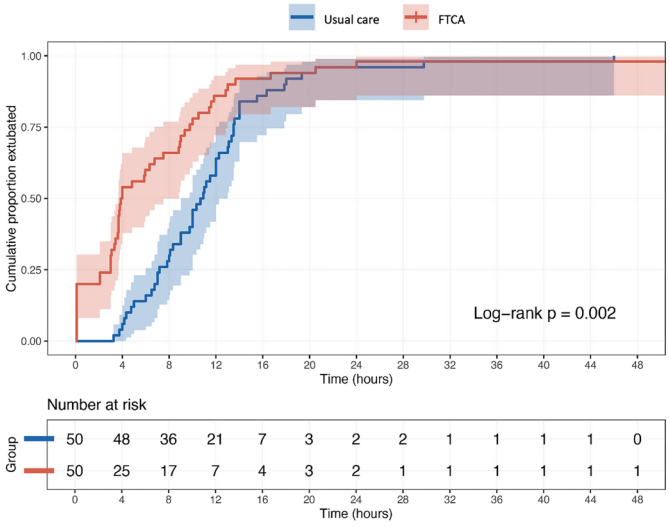


Figure 2 Time to tracheal extubation after ICU admission. Kaplan-Meier curves show the cumulative proportion of participants extubated over the first 48 hours after ICU admission. Participants extubated in the operating room were assigned a time of 0 hours. Participants who remained intubated beyond 48 hours or died before extubation were censored at 48 hours or at death, respectively. Groups were compared using the log-rank test. FTCA, fast-track cardiac anaesthesia; ICU, intensive care unit.

it does not preserve the randomised comparison and is presented descriptively.

Because the per-protocol population was identical to the intention-to-treat population, per-protocol estimates are identical to those reported above. In post hoc exploratory analyses, the direction and magnitude of the treatment effect on early extubation were consistent across hospitals (Hospital A: 57.1% vs 5.6%, risk difference 0.52, 95% CI 0.23 to 0.71; Hospital B: 51.7% vs 6.3%, risk difference 0.45, 95% CI 0.23 to 0.63; interaction p=0.80) and across subgroups defined by admission status (elective vs urgent) and age (interaction p=0.78 and p=0.73, respectively) (online supplemental file 2, tables S3 and S4). The apparent effect was larger among patients with EuroSCORE II below the median (interaction p=0.02); however, this subgroup contained no usual-care events, the estimate is based on sparse data, and it should be interpreted with caution.

Opioid consumption and pain

Postoperative opioid consumption was lower in the FTCA group at 24 hours, with a Hodges-Lehmann location shift of −6.0 mg (95% CI −10.8 to −1.0; p=0.018). At 48 hours, the location shift was −5.2 mg (95% CI −11.0 to 0.0; p=0.059). Severe pain occurred in 3 (6.3%) FTCA patients and 13 (27.7%) usual-care patients (risk difference −0.21, 95% CI −0.36 to −0.06; p=0.006).

Service outcomes

ICU and hospital LOS were similar between groups. Median ICU LOS was 79.0 hour in the usual care group and 58.2 hour in the FTCA group (location shift −13.9 hour, 95% CI −25.0 to 2.9; p=0.179). Median hospital LOS was 7.8 and 7.9 days, respectively (location shift 0.1 days, 95% CI −0.9 to 1.0; p=0.791). No ICU readmissions occurred.

Safety outcomes

Safety outcomes were broadly similar between groups (table 3). There were no statistically significant between-group differences in major postoperative complications, haemodynamic adverse events, respiratory depression, postoperative blood transfusion, antiemetic use or naloxone use. Deep sedation occurred in 3 (6.0%) usual care patients and no FTCA patients. Lowest postoperative haemoglobin and 24-hour chest drain output were similar between groups. One in-hospital death occurred in a usual-care patient on day 94 after randomisation during the index admission; no deaths occurred within 30 days in either group. Hospital re-presentation occurred in 3 of 50 participants (6.0%) in the FTCA group and 4 of 50 participants (8.0%) in the usual-care group (risk difference −0.02, 95% CI −0.14 to 0.09; p>0.999). Additional descriptive data on postoperative treatments and early postoperative physiological profiles are presented in online supplemental file 2, table S5.

DISCUSSION

In this two-centre pilot randomised trial of selected adults undergoing scheduled isolated CABG surgery, four of the five prespecified feasibility criteria (consent, successful study drug administration, absence of drug administration errors and participant retention) were met at both centres, with complete ascertainment of the primary clinical endpoint. The recruitment capacity criterion was met at Hospital B but not at Hospital A. The findings therefore support delivery of the FTCA pathway in enrolled participants but do not establish that all requirements for a definitive trial were met at both centres. Compared with usual care, the FTCA pathway was associated with a higher proportion of patients extubated within 4 hours of ICU admission, more frequent operating-room extubation, shorter time to extubation, lower postoperative rescue opioid requirements during the first 24 hours and less severe pain. Because the pharmacological bundle, sugammadex-based neuromuscular reversal and the structured extubation workflow were delivered together, these preliminary differences apply to the pathway as a whole rather than to its pharmacological components alone.

The extubation findings remained directionally consistent in the descriptive analysis excluding patients extubated in the operating room. However, that analysis conditions on a post-randomisation event and does not preserve the original randomised comparison. ICU and hospital LOS were not clearly reduced. The sample was too small to establish comparative safety or exclude uncommon adverse events.

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The distinction between initial screening and confirmed eligibility is important for interpreting recruitment feasibility. Although 80 patients at each centre met initial screening criteria, 41 at Hospital A and 17 at Hospital B were subsequently excluded after detailed assessment, so that recruitment capacity was based on 39 and 63 eligible patients, respectively. The observed rate at Hospital B exceeded the prespecified threshold, although its CI included values below that threshold. The high consent rate of 98.0% reflects acceptance among the 102 patients who remained eligible and were approached, of whom two declined, and does not offset the lower eligible-patient recruitment rate at Hospital A.

Screening workload also differed between centres: Hospital A screened 253 patients and randomised 39, whereas Hospital B screened 121 and randomised 61, equivalent to approximately 6.5 and 2.0 patients screened per participant randomised. No eligible patient was withheld from approach for staffing, investigator availability, workflow or clinician-preference reasons, but these two-centre observations cannot establish whether the differences in eligibility yield are attributable to hospital type or case mix. Recruitment projections for a definitive trial should therefore use centre-specific numbers remaining eligible after all criteria have been applied, together with consent rates and the associated screening workload, rather than initial screening counts or a pooled randomisation rate.

These findings are consistent with the rationale for ERAS, in which early extubation is considered an important component of recovery and ICU efficiency.[4 5] FTCA has long been used to support early extubation after cardiac surgery, but practice remains heterogeneous and the optimal pharmacological strategy remains uncertain.[6–11] The present trial adds prospective randomised pilot evidence for a structured pathway that combines multimodal pharmacology with protocolised extubation assessment.

The analgesic findings are also consistent with prior literature. Persistent opioid use after cardiac surgery occurs in approximately 5%–10% of previously opioid-naïve patients and is associated with chronic pain, impaired recovery and opioid-related harm.[12–15] Prior cardiac surgical studies have reported lower pain scores and reduced postoperative analgesic requirements with intraoperative methadone, likely reflecting its prolonged multimodal analgesic effects.[16–21] In this trial, lower postoperative rescue opioid requirements during the first 24 hours and less severe pain provide a preliminary signal of improved early analgesia with the pathway. These findings do not establish a reduction in total perioperative opioid exposure because the reported postoperative requirements excluded intraoperative methadone and other intraoperative opioids.

Other components of the bundle may also have contributed, including the titratable analgesia and rapid offset of remifentanil, the anti-hyperalgesic and opioid-sparing effects of magnesium and lignocaine,[22–27] and the cooperative sedation, sympatholysis and opioid-sparing analgesia of dexmedetomidine, which has been associated in some studies with shorter time to extubation, reduced ICU LOS and possible renal or delirium-related benefits, although findings are not uniform.[28–33 41] This trial was not designed to isolate individual drug effects. Rather, it evaluated a pathway-level intervention in which pharmacological choices, neuromuscular reversal, and the extubation workflow were delivered as a package, and the estimand addressed by the trial is accordingly the effect of implementing the complete pathway compared with current usual care.

Our previous retrospective cohort study suggested that a similar FTCA bundle was associated with earlier extubation, lower postoperative opioid use and shorter ICU LOS compared with usual care.[34] The current randomised pilot trial provides evidence that is less susceptible to confounding by indication and centre-level practice variation, but ICU and hospital LOS were not clearly reduced. This distinction is important: earlier extubation may indicate physiological readiness for recovery, but discharge timing is also shaped by bed availability, staffing, ward readiness, institutional discharge practices and competing service demands,[42 43] so length-of-stay outcomes may require broader workflow alignment before measurable reductions are seen.

The enrolled cohort had a median age of 70 years, was 87% male and had a median EuroSCORE II of 1.3 and median LVEF of 57%. The eligibility criteria selected patients with preserved left ventricular systolic function and low to moderate predicted operative risk, and the 58 exclusions after initial screening reflected protocol-defined criteria rather than operational barriers to approaching eligible patients. The high consent rate should therefore be interpreted within this selected population and not extrapolated to all patients undergoing CABG. The findings generalise most directly to similarly selected patients undergoing scheduled isolated CABG at centres with comparable perioperative infrastructure. Broader eligibility in a definitive trial would require clinical justification and prospective assessment of recruitment capacity, together with systematic collection of race and ethnicity data.

Strengths and limitations

This study has several strengths. It used a randomised design, concealed allocation, blinded endpoint assessment, complete follow-up and intention-to-treat analysis. The intervention was protocolised but pragmatic, reflecting real-world cardiac anaesthesia practice across one public and one private hospital. Effect estimates were reported using risk differences for binary outcomes and Hodges-Lehmann location shifts for continuous outcomes, improving interpretability in a pilot trial with a modest sample size.

Several limitations should be acknowledged. The sample size was small and chosen to assess feasibility and preliminary efficacy signals rather than definitive treatment

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effects. Eligibility was restricted to selected CABG patients with preserved left ventricular systolic function and low to moderate operative risk, limiting generalisability to higher-risk patients, emergency surgery, redo procedures, valve surgery or complex aortic surgery. Treating anaesthetists could not be blinded, although surgeons, intensivists, nurses, data collectors, outcome assessors and the statistician were blinded; because allocation could potentially have been inferred from the intraoperative anaesthetic record, and the success of blinding among intensive care clinicians was not formally assessed, performance bias affecting the clinician-determined primary endpoint cannot be excluded.

The trial tested a bundle and cannot determine the independent contribution of methadone, dexmedetomidine, remifentanil, magnesium, lignocaine, sugammadex-based reversal or the extubation workflow. Uncommon harms could not be reliably excluded, particularly methadone-related prolonged sedation or arrhythmogenicity and dexmedetomidine-related bradycardia or hypotension; furthermore, haemodynamic safety outcomes were ascertained as sustained or intervention-requiring events by daily record review rather than by continuous electronic capture of any threshold excursion, and the absence of recorded bradycardia and hypotension events should be interpreted in that light. The sensitivity analysis excluding operating-room extubation conditions on a post-randomisation event is descriptive only.

Two prespecified efficacy outcomes, disability-free survival and the postoperative quality of recovery score, were not assessed because dedicated funding was unavailable for research nursing support to undertake structured follow-up using validated instruments. This represented a departure from the planned outcome assessment and limits evaluation of longer-term functional recovery. Consequently, we could not determine whether the observed improvements in early postoperative outcomes were accompanied by improved quality of recovery or disability-free survival. Finally, data on race and ethnicity were not recorded.

Recruitment feasibility was not demonstrated uniformly across centres. In addition to the observed shortfall at Hospital A, the CI around the rate at Hospital B included values below the recruitment threshold. The absence of post-randomisation dropout also requires cautious interpretation: the overall exact 95% CI was 0.0% to 3.6%, and therefore did not exclude an underlying dropout rate of 2% or higher. Meeting a criterion on the basis of its observed point estimate should not be interpreted as precise confirmation of performance in a larger trial.

Implications and future research

The FTCA pathway was delivered with high consent, complete study drug administration, no drug administration errors and no post-randomisation dropout in this selected population. The preliminary extubation and analgesic findings warrant further evaluation, but the recruitment shortfall at Hospital A should be addressed when planning a definitive trial. Prospective screening at candidate centres should distinguish patients who meet initial screening criteria, those who remain eligible after detailed assessment, those approached for consent and those randomised. These centre-specific estimates should inform the number of participating centres, recruitment duration and screening resources. Any broadening of eligibility should be justified clinically and assessed prospectively rather than assumed to resolve the recruitment shortfall.

A definitive trial should include centres with different perioperative practices and consider broader cardiac surgical populations where clinically appropriate. Outcomes should extend beyond extubation time to include quality of recovery, delirium, persistent opioid use, functional status, health-related quality of life, disability-free survival, resource utilisation, cost-effectiveness and implementation outcomes.[42 44] The trial should incorporate a formal assessment of blinding among clinicians who determine extubation timing and stratify randomisation by site. Because the intervention is pathway-based, future trials should measure fidelity, contamination, staff workload and barriers to adoption. Cluster randomisation by centre, anaesthetic team or implementation unit could be considered if contamination between treatment strategies is likely. These pilot findings do not support routine adoption before definitive evaluation of effectiveness and safety.

CONCLUSION

In selected adults undergoing scheduled isolated CABG surgery, four of the five prespecified feasibility criteria were met at both centres, but the recruitment capacity criterion was met only at Hospital B. The FTCA pathway was associated with earlier extubation, lower postoperative rescue opioid requirements during the first 24 hours and less severe pain compared with usual care. These preliminary findings apply to the integrated pathway and do not establish the independent effects of its pharmacological components. The trial was not sufficient to establish comparative safety or exclude uncommon harms. A definitive pragmatic multicentre trial requires centre-specific recruitment planning and should evaluate patient-centred recovery, safety, resource utilisation and implementation outcomes before routine adoption.

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