Intravenous methadone for sternotomy pain control in cardiac surgical patients: a randomized controlled trial

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BACKGROUND

PAIN IN CARDIAC SURGERY

Despite modern day improvements in pain treatment and availability of different analgesic modalities, suboptimal postoperative pain control remains an issue in cardiac surgical patients. Acute postoperative pain is common among cardiac surgical patients, particularly within the first 2 days after surgery, with reported at least moderate intensity.[1] There could be many facets for postoperative pain after adult cardiac surgery. Pain can be caused by surgical incisions and dissections, sternal fracture or incomplete bone healing, multiple drainage cannulas and chest tubes and sternal wound infections.[2-4] Poorly controlled acute postoperative pain is associated with adverse physiological outcomes that impair the recovery of cardiac surgical patients. It is associated with decreased patient satisfaction, delayed postoperative ambulation, and the development of chronic postsurgical pain (CPSP).[5] The association between sternotomy pain and pulmonary complications has been observed, and the sympathetic activation secondary to pain can induce myocardial ischemia and arrhythmias.[6-7] Pain control has also been pointed out as one of the major concerns to cardiac surgical patients in intensive care unit.[8] Therefore, optimal acute pain control not only can improve clinical outcomes, but also improves patient satisfaction after cardiac surgery.

Postoperative pain that persists beyond the normal time for tissue healing is increasingly recognized as an important complication after various types of surgery. According to the International Association for Study of Pain, CPSP is defined as the persistence of pain at surgical site or referred area, at least 3 months following the surgical procedure.[9] CPSP is common after cardiac surgery. The reported incidence was 28% to 56% up to 2 years postoperatively.[10-12] Several mechanisms have been involved in the development of chronic pain after sternotomy. These include dissection, nerve entrapment by sternal wires, sternal retraction, ribs fractures, and intercostal neuralgia as a consequence of nerve damage during dissection of the internal mammary artery during coronary artery bypass graft (CABG).[2-3] In addition, poorly controlled pain has been a general risk factor for the development of CPSP. All can stimulate the release of pro-inflammatory cytokines which sensitize the afferent nociceptive fibres to cause chronic pain. CPSP has the potential to impact daily functioning and quality of life of patients, as well as increasing the healthcare costs. CARDpain study reported that among those with CPSP, over 50% had significant pain-related interferences with activities of daily living (family and home responsibilities, recreation and employment) at 3, 6 and 12 months following cardiac surgery.[13] Therefore, apart from optimal acute pain control, it is equally

important to prevent and manage CPSP, to ensure better satisfaction and quality of lives for our patients.

CHALLENGES IN PAIN MANAGEMENT

Intravenous opioids such as fentanyl and morphine have been the mainstay of perioperative analgesia for cardiac surgery, either by intermittent boluses or through a patient-controlled device. The primary problem with this mechanism of delivery is that significant fluctuations in serum opioid concentrations can occur, resulting in effects which range from inadequate analgesia to overdose and respiratory depression. These peaks and troughs of analgesia that occur with intermittent opioids administration may explain the suboptimal pain control during the initial postoperative period. In contrast to intermittent administration of short-acting opioids such as morphine and fentanyl, a single dose administration of methadone can be considered. Methadone was conventionally used in cancer and chronic pain management. It can be administered via oral, intravenous, and other parenteral routes. Despite being an often-used alternative to morphine, it remains relatively invisible in perioperative settings. Methadone is a unique opioid that may provide several important potential benefits for surgical patients in the perioperative period. It is a potent mu receptor agonist with a rapid onset and longest half-life (24-36 hours) of the clinically used opioids. According to a pharmacokinetic study,[14] central nervous system effect site methadone concentration rapidly equilibrates with plasma concentrations, evidenced by a short lag time between plasma concentrations and effects ($t_{1/2}k_{e0}$ 4min). This is comparable to the rapid onset and effect compartment equilibration of fentanyl and sulfentanil (5-6min), and in contrast the slow onset time of morphine, where $t_{1/2}k_{e0}$ has been reported to exceed 4 hours.[15] In addition, as reviewed in an editorial, when methadone is administered at a dose of 20mg or higher, the duration of analgesia approximates the half-life of 24-36 hours. Therefore, a single intravenous dose 20mg administered to an adult at induction of anaesthesia should provide a rapid onset and significant pain relief up to 1-2 days postoperatively, which is the period reported to have the highest pain score after cardiac surgery. Methadone is also a N-methyl-D-aspartate (NMDA) receptor antagonist. It has been reported to possess anti-hyperanalgesic and anti-allodynic properties, that is important in preventing pain sensitization and the development of CPSP,[16-17] which is of high risk in cardiac surgical patients.

SIDE EFFECTS OF METHADONE

Methadone shares the same opioid-related side effects as with many other opioids such as nausea and vomiting, drowsiness and respiratory depression. According to a meta-analysis in 2020 which

included seven randomized controlled trials on intraoperative use of intravenous methadone[18], four studies reported no adverse events. One study reported that the patients who received intraoperative methadone experienced more sedation compared to control group at 24 hours after surgery. One study reported that the intraoperative morphine group had more sedation compared to methadone group during the postoperative period. Methadone was not shown to have a higher incidence of postoperative nausea and vomiting compared to the morphine group. Methadone has been reported to be associated with cardiac conduction abnormalities such as QT prolongation, QT interval dispersion and cardiotoxicity (Torsade de pointes).[19] However, most of the cardiac-related side effects were seen in patients on prolonged or maintenance treatment with methadone. Significant dose-dependent QTc prolongation usually occurs at a high dose of methadone. A single injection of intravenous methadone at low dose is unlikely to result in significant cardiotoxicity. No cardiac disturbances were reported from the meta-analysis.[18]

GAPS IN THE LITERATURES

Only a few trials have studied intravenous methadone as an analgesic in surgical patients, in particular, there have not been many studies in the field of cardiac anaesthesia. A randomized controlled trial done by Murphy et al showed intraoperative methadone to be superior to fentanyl for patients undergoing cardiac surgery.[20] Methadone was demonstrated to reduce morphine consumption in the first 24 postoperative hours and improved pain scores at 12h after extubation compared to patients receiving fentanyl. There was 40% reduction in morphine requirement during the first 24h after extubation, and the severity of postoperative pain was decreased by 30-40% during the first three days after cardiac surgery. There was only one study comparing the analgesic efficacy between methadone and morphine give at the time of induction in cardiac surgical patients.[21] Methadone was shown to reduce opioid requirement at 24h postoperatively and significantly reduce the incidence of postoperative nausea and vomiting. So far there has not been any studies on using methadone for cardiac surgery in Chinese populations, and none on the role of methadone for prevention of chronic post-surgical pain in cardiac surgical patients. Substantial literatures have demonstrated the ethnic differences in pain perception and endogenous pain modulation is postulated to be a mechanism for ethnic differences. Studies comparing Caucasians and Asians, such as Chinese and Indians, generally demonstrated lower pain tolerance in Asian populations.[22-23] The primary aim of this study is to evaluate the use of methadone on acute and chronic pain control after open cardiac surgery, compared with conventional opioid-based approach using morphine and fentanyl.

METHODS/DESIGN

Study population and design

This is a single-centre, double-blinded, pilot randomized controlled trial conducted at Prince of Wales Hospital, a university teaching hospital with 1650 beds in Hong Kong. All elective cardiac surgical patients will be admitted to a 23-bed ICU for early postoperative care and monitoring with 1:1 nursing at all times, with an expectation of discharge from ICU to a high-dependency cardiac ward within 24 hours after surgery. Currently 350-400 adults undergo elective coronary artery bypass graft and/or valvular surgery each year.

Randomization and concealment

Patients will be randomized to receive either methadone 0.2mg/kg (maximum dose 20mg) or equipotent dose of morphine, adding to a syringe containing saline made up to 50ml in total, by drawing sequentially numbered, coded sealed, opaque envelops each containing the group assignment of either methadone or morphine group. The sealed envelopes for randomization will be prepared by a third party who takes no further part in the study. The study syringes containing the drug solution will be prepared by a nurse not involved in the study with blind labelling. The primary care team, blinded to the group allocation, will perform all surgical procedures using standardized techniques. Anaesthetists and nurses blinded to group allocation will record data intraoperatively, in ICU, and at regular intervals in the cardiac wards.

Eligibility criteria

We will include adult patients age 18 or older, undergoing elective coronary artery bypass graft (CABG), valve repair/replacement, or combined CABG/valve procedure via sternotomy, with an expected extubation within 12 hours of surgery. The exclusion criteria include emergency surgery, aortic surgery, redo surgery, preoperative renal failure requiring renal replacement therapy or creatinine clearance <30ml/min (calculated by Cockcroft-Gault formula), liver dysfunction (liver enzymes twice upper limit normal), LVEF <40%, requirement of mechanical hemodynamic support in perioperative period, history of chronic pain or who regularly used pain medications (except paracetamol and non-steroidal anti-inflammatory drugs), history of psychiatric illnesses or illicit drug use, intraoperative use of remifentanil and unable to provide informed consent.

Anaesthesia and interventions

All patients will receive standard monitoring for cardiac surgery. General anaesthesia will be induced with midazolam 0.01-0.05mg/kg, fentanyl 2-5mcg/kg and rocuronium 0.5-1mg/kg to facilitate intubation with single-lumen cuffed endotracheal tube. Anaesthesia will be maintained with sevoflurane and propofol infusion that target Bispectral Index 40-60. The study drug (either methadone 0.2mg/kg or morphine at equipotent dose) in blind labelling will be administered at time of induction by intravenous infusion over 30 minutes. No further morphine will be given throughout the operation. No other analgesics (paracetamol, non-steroidal anti-inflammatory agents, dexmedetomidine, ketamine), steroids or antiemetics will be given intraoperatively. Patient-controlled analgesia (PCA) morphine protocol will be prescribed to patients for 72 hours after operation for postoperative analgesia. Oral analgesics including paracetamol 1g every 6 hours and dihydrocodeine 30mg three times a day will be prescribed by parent surgical team. At the end of the operation, the patients will be kept sedated with propofol infusion to ICU. Propofol infusion will be stopped upon admission to ICU to facilitate weaning from ventilator. Adaptive Support Ventilation (ASV) is used in ICU for weaning which adjusts the ventilation parameters depending on the patient's lung mechanics and effort. Pain will be assessed by nurses in ICU at 4h after stopping sedation, then once every 2h. Upon extubation, patient will be assessed the pain score and the level of sedation at 15min, 8h, 12h, 24h, 48h and 72h. 1mg morphine will be administered via PCA to patients if pain of more than mild severity was noted. Any nausea or vomiting, and use of rescue antiemetics will be documented.

Outcome measures

Primary outcomes

The most intense pain typically occurs in the first 2-3 days after open heart surgery, leading to greater need for analgesia during this period. The primary outcome will be set at 72-hour time frame based on the postoperative morphine consumption.

Secondary outcomes

Key secondary outcomes include the postoperative pain scores measured by numerical rating scale (NRS) represented as AUC at rest and movement; the time successfully weaned to spontaneous breathing according to ASV; patient satisfaction score to pain within 72h after the operation; time to first morphine rescue; side effects of opioids including the number of episodes of postoperative nausea and vomiting; time to first bowel movement; the recovery from surgery in terms of length of ICU and hospital stay; and chronic postsurgical pain at 3 and 6 months assessed using the Douleur Neuropathique en 4 questionnaire (DN4). It is a ten items questionnaire and the Mandarin Chinese

version has been validated in previous study. [26] Each item of DN4 is assigned a score of 0 when the participant answered 'no' and a score of 1 when the participant answered 'yes'. The total DN4 score ranges from 0 to 10, and a score ≥ 4 indicates a diagnosis of neuropathic pain. [27-28]

Data collection

Patients will be screened the day before operation for eligibility. Eligible patients will be given the patients' information sheets regarding the main aspects of the trial. Research nurses will then discuss with the patients in light of the information provided in the information sheets. Written informed consent will be obtained from patients willing to participate in the trial. All data is collected by research team members blinded to group assignment. Patient demographics and body mass index will be recorded. The time weaned to spontaneous breathing on ASV will be recorded. At 15min after tracheal extubation and at 8h, 12h, 24h, 48h and 72h post-extubation, pain score at rest and on coughing will be quantified using Numerical Rating Scale (NRS) from 0 to 10. Zero represents no pain at all while 10 points represents the worst pain ever. The time to first morphine rescue (in minutes after surgery) will be measured. The level of sedation will be measured using the Ramsay Sedation Scale (1 = anxious, agitated or restless, or both; 2 = co-operative, oriented and tranquil; 3= respond to command only; 4 = exhibit brisk response to light glabellar tap or loud auditory stimulus; 5 = exhibit sluggish response to light glabellar tap or loud auditory stimulus; 6 = exhibits no response), episodes of nausea and vomiting, and whether antiemetics are prescribed will also be recorded at the above time points. At the same time, patients will be asked to rate the overall satisfaction with pain management on a verbal analogue scale (0 = worst possible, 100 = best possible).

The Douleur Neuropathique en 4 questionnaire (DN4)[26] will be used to evaluate the presence of neuropathic pain at 3 and 6 months after surgery.

The following medical and surgical data during the hospital stays will be extracted from patient charts:

1. Patient demographics (age, gender, EuroScore)
2. Type of surgery
3. Duration of surgery and duration of cardiopulmonary bypass
4. ASV time to spontaneous breathing
5. Total morphine consumption at 24 and 72 hours after surgery
6. Episodes of nausea and vomiting, and use of rescue antiemetics
7. Length of ICU and hospital stay

		STUDY PERIOD								
	Enrolment	Post-allocation								
TIMEPOINTS	Baseline	OT	4h stop sedation	15min extubate	12h extubate	24h extubate	48h extubate	72h extubate	3-month postop	6-month postop
ENROLMENT:										
Eligibility screen	X									
Informed consent	X									
Demographic data	X									
Comorbidity data	X									
EuroScore	X									
Allocation	X									
INTERVENTIONS										
Intraoperative methadone		X								
Intraoperative morphine		X								
OUTCOMES:										
Ramsay sedation scale			X	X	X	X	X	X		
NRS score			X	X	X	X	X	X		
ASV time to spontaneous breathing				X						
DN4									X	X
Time to first morphine rescue					X	X	X	X		
Postoperative morphine consumption					X	X	X	X		
Patient satisfaction					X	X	X	X		
Use of rescue antiemetics					X	X	X	X		
Nausea/vomiting					X	X	X	X		
Time to first bowel movement					X	X	X	X		
ICU and hospital stay								X		

Figure 1 Assessments overview. NRS, numerical rating scale; ASV, adaptive support ventilation; NPQ, Neuropathic Pain Questionnaire; HK-PCS, Pain Catastrophizing Scale Hong Kong version.

Blood sampling for methadone level

Venous blood samples (5ml) will be obtained at 0, 1, 2, 4, 6, 8, 10, 12, 24, 48, 72 and 96 hours after administration of methadone. Plasma concentration of methadone will be determined by LC-MS/MS (ESI pos). The internal standard (7-dimethylamino-5,5-diphenyl-4-octanone, 2.5ng) will be added to plasma (0.5ml), which will be acidified and then processed by SPE (Waters Oasis MCX cartridges).

Sample size calculation and statistical methods

The sample size is calculated using G*Power software version 3.1.9.3 (Kiel University, Kiel, Germany), and based on postoperative morphine consumption at 24 hours, which is the primary outcome variable. Because there was no randomized controlled trial on use of methadone in cardiac surgery in Asian population, a pilot study (50 patients) was conducted from cardiac surgical patients in Prince of Wales Hospital, Hong Kong. The mean (SD) postoperative morphine consumption at 24 hours was 21.5 (8.2) mg in patients receiving methadone, whereas that for morphine group was 30.3 (14.0) mg. With an alpha probability of 0.05 and a power of 90%, a sample size of 34 patients in each group will be needed. Assuming 15% drop-out rate, the sample size is increased to 86 patients. The primary analyses will be performed on a modified intention-to-treat basis. Patients will be analysed according to their randomized allocated groups but will be excluded from the analysis if they do not adhere to the protocol after randomisation. Categorical data are reported as numbers and percentages. Continuous variables are reported as mean (standard deviation) or median (interquartile range) as appropriate after checking for normality using the Shapiro-Wilk's test. Comparison of continuous data is performed by Student's *t* test and by Mann-Whitney U test for non-normally distributed data. Chi-square test is used to compare groups with categorical variables. Level of significance is set at $P<0.05$. SPSS 27.0 software (IBM Corp, Armonk, NY) will be used for data analysis.

DECLARATIONS

Consent to participate

All participants will provide written informed consent. All research will be conducted in accordance with the Declaration of Helsinki and all other relevant guidelines and regulations.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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