BMJ Open

Comparison of dexmedetomidine and meperidine for the prevention of shivering following coronary artery bypass graft (CABG): a randomised controlled study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-053865
Article Type:	Protocol
Date Submitted by the Author:	26-May-2021
Complete List of Authors:	Cao, Cuicui; First Affiliated Hospital of Shandong First Medical University, Lv, Meng; First Affiliated Hospital of Shandong First Medical University, Department of Anesthesiology Wei, Chuan; First Affiliated Hospital of Shandong First Medical University, Department of Anesthesiology Yan, Jie; First Affiliated Hospital of Shandong First Medical University Gu, Chang; First Affiliated Hospital of Shandong First Medical University, Department of Anesthesiology Wang, Yue; First Affiliated Hospital of Shandong First Medical University, Department of Anesthesiology
Keywords:	Anaesthesia in cardiology < ANAESTHETICS, Coronary heart disease < CARDIOLOGY, Cardiac surgery < SURGERY, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

Comparison of dexmedetomidine and meperidine for the prevention of shivering following coronary artery bypass graft (CABG): a randomised controlled study

Cui-cui Cao[1#], Meng Lv[1#], Chuan-song Wei[1], Jie Yan[1], Chang-ping Gu[1]*, Yue-lan Wang[12]*

[#]Co-First author

***Co-Responding author 1 Department of Anesthesiology, The First Affiliated Hospital of Shandong First Medical University**

2 Shandong Provincial Qianfoshan Hospital, Shandong Institute of Anesthesia and Respiratory Critical Medicine, Jinan, China

cccbzyxy@163.com qylvmeng@163.com song6798@126.com

yj17ylh@163.com changpinggu@163.com wyldgf@163.com

Corresponding author Chang-ping Gu, No.16766, Jingshi Road, Jinan, Shandong Province, China, changpinggu@163.com, 15806607957; Yue-lan Wang, No.16766, Jingshi Road, Jinan, Shandong Province, China, wyldgf@163.com, 15953105780

ABSTRACT

Introduction Shivering is one of the common complications during the perioperative period. There are few studies of pharmacological interventions for the prevention of shivering following CABG. Both dexmedetomidine and meperidine are effective in prevention of postanesthetic shivering. This study aims to explore the efficacy and safety of dexmedetomidine for preventing shivering after CABG and to compare the effects of dexmedetomidine and meperidine on the incidence of shivering in patients undergo CABG.

Methods and analysis This study is a single center, prospective, randomised, double-blinded, non-inferiority clinical trial. A total of 180 patients aged 18 to 75 years, American Society of Anaesthesiologists'(ASA) II-IV, undergoing elective CABG will be included in this study. Patients will be randomly assigned into dexmedetomidine group, meperidine group and control group in an intended 1:1:1 allocation ratio. The patients will be followed up for 7 days after surgery. The primary outcome is the incidence of shivering within postoperative 24 hours. The secondary outcomes are the times of remedial drugs used after surgery, the incidence of postoperative hypotension and bradycardia, sedation scores, extubation time of endotracheal tube, intensive care unit (ICU) length of stay, the incidence of postoperative delirium within 7 days after surgery, the incidence of postoperative arrhythmias, the incidence of postoperative

nausea and vomiting (PONV), the average hospital length of stay, and the mortality rate 30 days after the operation.

Ethics and dissemination This study protocol has been approved by the ethics committee of The First Affiliated Hospital of Shandong First Medical University on 20 January 2021 (YXLL-KY-2021(002)) and registered at ClinicalTrials.gov. The results of this study will be presented at national and international scientific meetings or conferences. We plan to publish the data in peer-reviewed international scientific journals.

Trial registration number NCT04735965

Keywords Shivering dexmedetomidine meperidine CABG

Article Summary

Strengths and limitations of this study

1.The intervention is double-blinded.

2.This is a well-designed randomised controlled trial to explore the effectiveness and safety of dexmedetomidine for the prevention of postoperative shivering in patients undergo elective CABG, and to compare the effectiveness of dexmedetomidine and meperidine on the incidence of shivering in patients undergo CABG.

3.The double-blinded and placebo-control design will enhance objectivity and help reduce bias.

4.This is a single-centre clinical study.

5.Only early outcomes will be assessed including the incidence of shivering and other endpoints up to 30 days after the operation.

INTRODUCTION

Shivering is one of the common complications of the patients during the perioperative period, it has been reported to range from 5% to 65% in general anaesthesia and 33% during epidural anaesthesia.[1] The most common cause of shivering are hypothermia, blood transfusion and pain. Patients with hypothermia after CABG surgery (<36ºC) usually have a higher mortality rate and prolonged hospital length of stay.[2]

Shivering can increase the perioperative risk of patients with coronary artery disease due to the increased oxygen consumption (by 100–600%), especially the risk of myocardial ischemia. Moreover, the interference with monitoring of electrocardiography (ECG) and blood pressure, the increase of intracranial and intraocular pressure, increased production of carbon dioxide and circulating catecholamines are also the side effects.[3 4] Therefore, it is important to prevent shivering after CABG. The incidence of postoperative shivering is still high, although some non-pharmacological methods such as heating blanket or warming the administered fluid has been used after the surgery.[5] Some medical agents such as nefopam, tramadol, meperidine (pethidine), clonidine, morphine, fentanyl, doxapram, ketamine, nalbuphine were reported effective in preventing postanesthetic shivering.[3 6-11] But

there are few studies of pharmacological interventions used for preventing shivering after CABG.

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist with an eight times higher affinity for 2-adrenoceptor than clonidine which can cause sedation, analgesia, anxiolysis and attenuation of the neuroendocrine and hemodynamic responses to anesthesia and surgery.[12 13] It may also provide a deeper level of sedation, decrease the incidence of PONV, and increase hemodynamic stability during a sudden increase in stress.[14] Previous studies have shown that dexmedetomidine can reduce the incidence of shivering after both spinal anesthesia and general anesthesia.[14] But the effects of dexmedetomidine on the incidence of shivering has not been reported in patients after CABG.

Meperidine is a combined μ- and κ- receptor agonist. And it stimulates μ receptors to exert analgesic effect. It can prevent hypothermia with peripheral vasoconstriction and central vasodilatation. Numerous trials have confirmed that meperidine was effectively used for the prevention and treatment of perioperative shivering.[15 16] But the anti-shivering mechanism of meperidine is still unclear. And meperidine also has some side effects such as nausea, vomiting, respiratory depression especially in patients who had previously used opioid or anesthetics, and hallucination.[17] Therefore, it is important to find an effective agent therapy for preventing postoperative shivering with less side-effects in patients undergo CABG.

The aim of this study is to explore the efficacy and safety of dexmedetomidine for preventing shivering after CABG and to compare the effects of dexmedetomidine and meperidine on the incidence of shivering in patients undergo CABG.

METHODS AND ANALYSIS

Study design:

This study is a prospective, single-centre, non-inferiority, double blinded, randomised and placebo-controlled trial with three parallel arms (figure 1). It is designed to allocate patients in an intended 1:1:1 allocation ratio to test the efficacy and safety of dexmedetomidine for the prevention of postoperative shivering in patients undergo elective CABG, and to compare the effectiveness of dexmedetomidine and meperidine on the incidence of shivering in patients undergo CABG.

This study is conducted according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), and SPIRIT 2013 Checklist has been included in online additional file 1.

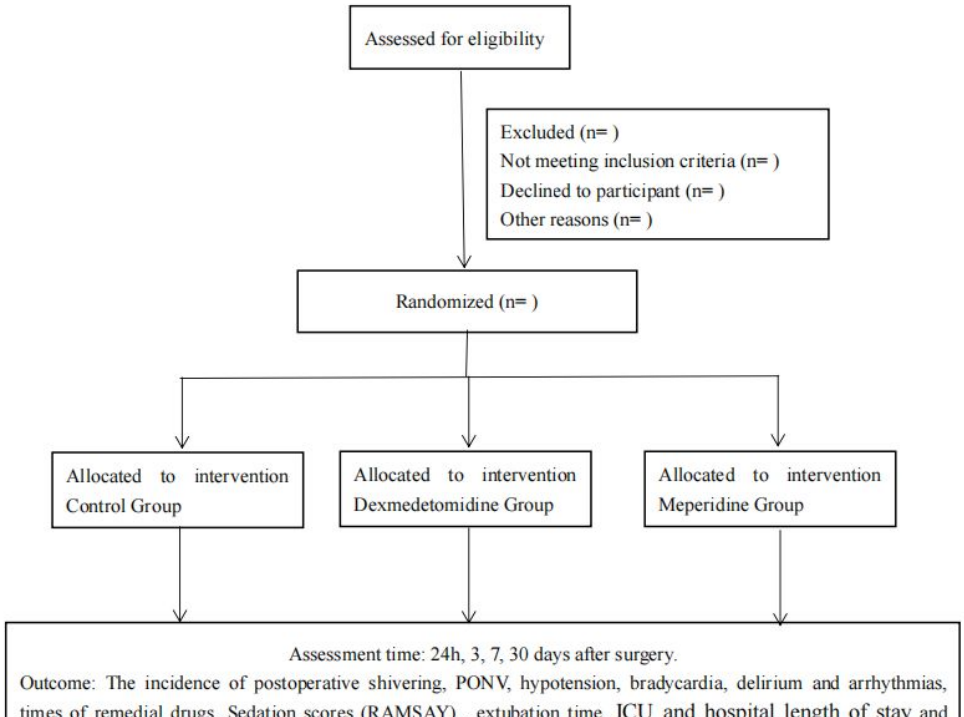


Figure 1 Consolidated Standards of Reporting Trials flow diagram. PONV, postoperative nausea and vomiting; ICU, intensive care unit.

Study setting

This study will be performed in The First Affiliated Hospital of Shandong First Medical University.

Participants

Inclusion criteria

Participants with the following criteria are eligible for the study: (1) patients aged between 18 and 75 years, (2) patients undergoing elective coronary artery bypass graft, (3) ASA II-IV grade, (4) in accordance with ethics, patients voluntarily participate in the trial and signed the informed consent for the clinical study.

Exclusion criteria

Participants meet one or more of the following criteria are excluded from the study: (1) patients with neurological or psychiatric disorders, (2) hepatic and renal dysfunction, (3) severe hyperthyroidism or hypothyroidism, (4) The temperature of patients greater than 38℃ or less than 36℃, (5) postoperative hemodynamic instability, (6) preoperative use of left ventricular assistance device, (7) Patients with severe diabetic

complications (diabetic ketoacidosis, hyperosmolar coma, various infections, diabetic nephropathy), (8) Patients who have participated in other clinical studies within 3 months.

Intervention

A total of 180 patients will be randomly allocated to Dexmedetomidine group (group Dex, n=60), Meperidine group (group M, n=60) and control group (group P, n=60). Standard monitoring including ECG, non-invasive blood pressure (NIBP) and oxygen saturation (SPO_2) will be used in all patients, radial artery catheterization and central venous catheterization will also be conducted. The pulse rate, arterial blood pressure, peripheral arterial oxygen saturation and nasopharyngeal temperature will be continuously monitored and recorded at the time before study drug administration (baseline) and 15,30, 60, 90 minutes after study drug administration. Neuromuscular block monitor will be monitored by using a peripheral nerve stimulator intraoperatively. The temperature of the operating room and ICU will be maintained at 22–25 ℃.

All patients will not receive premedication prior to induction of anesthesia. Anesthesia will be induced with midazolam (0.05 mg/kg), propofol (1-2 mg/kg), sufentanil (0.3 μg/kg) and atracurium (0.8 mg/kg) to facilitate tracheal intubation. Propofol and remifentanil will be continuously used during the surgery, and atracurium (0.4 mg/kg) will be added if required.

In group Dex, 1 μ g/kg dexmedetomidine will be continuously infused over 15 minutes. In group M, patients will receive meperidine 0.5 mg/kg intravenously. In group P, patients will receive the same volume of normal saline according to the dose of the two groups above.

Dexmedetomidine and meperidine will be given to the patients 30 minutes before the end of surgery. If the shivering score developed to more than 2, 20 mg meperidine will be injected intravenously. Patient-controlled intravenous analgesia (PCIA) will be used for postoperative analgesia. Sufentanil, ondansetron, dezocine and saline were added into PCA pump to a total of 100ml (the dose of all the anagesia agents are used according to the patient's age and body weight). The PCIA is set at infusion rate of 2 ml/h, a bolus dose of 0.5 ml with a lock-out interval of 15 minutes. And the PCIA will be used immediately after the operation to postoperative 48 hours. No reversal agents will be administered. All patients will be transferred to ICU immediately after the surgery.

Outcomes

Primary outcome:

The primary outcome of this study is the incidence of shivering within postoperative 24 hours.

Secondary Outcomes:

1. Times of remedial drugs used after surgery within postoperative 24 hours.
2. The incidence of postoperative hypotension and bradycardia within postoperative 24 hours. Hypotension is defined as blood pressure less than 20% of baseline or systolic

blood pressure is lower than 90 mmHg. Heart rate greater than 100 beats or less than 60 beats per minute is defined as tachycardia and bradycardia, respectively.

3. Sedation scores: Ramsay Sedation Scale[18] will be used to assess the sedation score within 3 days after surgery.

4. Other adverse events: the incidence of postoperative arrhythmias within postoperative 24 hours, the incidence and severity of PONV within postoperative 3 days and the incidence of delirium within postoperative 7 days will be evaluated.

5. Extubation time of endotracheal tube after operation, ICU length of stay, hospital length of stay and postoperative all-cause mortality within postoperative 30 days will also be recorded.

Participant timeline

Eligible participants' screening can be performed during the preoperative visit the day before surgery. All patients volunteered to participate in this study and signed the informed consent. Randomisation will implement shortly before surgery, patients will be allocated to group Dex, group M and group P according to the random number table method. All patients will accept CABG surgery under combined intravenous-inhalation anesthesia. All study drugs will be administered 30 minutes before the end of surgery. All patients will be transferred to the ICU after surgery. The patients will be visited daily on the first 7 postoperative days by an investigator. Each visit will be documented which consist of an assessment of shivering, rescue drugs used, hypotension and bradycardia, PONV, sedation scores, delirium, arrhythmias, ICU and hospital length of stay and postoperative all-cause mortality within 30 days. (figure 2)

		STUDY PERIOD								
	Enrolment	**Allocation**	**Post-allocation**					**Close-out**		
TIMEPOINT	**$-t_1$**	**0**	**t_1**	**t_2**	**t_3**	**t_4**	**t_5**	**t_6**	**After end of participation**	
ENROLMENT:										
Eligibility screen	×									
Informed consent	×									
Allocation		×								
INTERVENTIONS:										
group Dex			←	→						
group M			×							
group P										
ASSESSMENTS:										

Incidence of shivering					×					
Times of postoperative rescue drugs used					×					
Incidence of hypotension and bradycardia					×					
Sedation scores （RAMSAY）						×				
Incidence of delirium							×			
Incidence of arrhythmias					×					
Incidence of PONV						×				
ICU and hospital length of stay								×		
Postoperative all-cause mortality								×		

Figure 2 Standard Protocol Items: Recommendations for Interventional Trials.
-t_1, the day before surgery; 0, day of surgery; t_1, 30 minutes before the end of surgery; t_2, 15 minutes after study drugs administration; t_3, within postoperative 24 hours; t_4, within postoperative 3 days; t_5, within postoperative 7 days; t_6, within postoperative 30 days.

Sample size

Regarding the sample size, we made a calculation of statistical power prior to the study. We set the statistical power of 0.80 and one-sided type I error of 0.05. Patients will be randomly assigned into group Dex, group M and group P in equal ratio. According to previous studies, we assume the incidence of shivering in group Dex and group M was 23% and 46.48%, respectively.[13 19] Based on these parameters, we can calculate the sample size of 55 patients per group. To compensate for potential dropouts or inadequate procedures, we assume shedding rate of 5%, determine that 60 patients in each group, to make a total of 180 patients.

Recruitment

Participants who meet the inclusion criteria will be recruited. The purpose, the procedures involved, the potential risks and benefits of this study will be described to each patient, and written informed consent will be obtained from the patient. If the patient cannot provide consent, written informed consent will be obtained from their

authorised representatives. The patient will be assured that they are free to decline consent without consequences, and they can withdraw consent at any time without affecting treatment.

Allocation

The participants will be randomly (computer-generated random number list) allocated to either group Dex or group M or group P with a 1:1:1 allocation ratio. An investigator not involved in participant registration and data collection will generate the allocation sequence using a computer random number generator. This allocation sequence will not be disclosed to ensure concealment until the completion of the trial.

According to the allocation sequence, a research assistant prepares the study drugs, and the following experiments will be conducted by the investigator without knowing the information of the study drugs.

Blinding

Both the patients and the investigators who participate in the intervention, observation and assessment of this research will be unaware of the study drugs assignment and group allocation until results have been analysed. All the study drugs will be administrated in identical appearances and labels. During the study, group allocation can be unmasked in order to protect the patient's safety. We can implement an urgent unmasking if considered necessary for the sake of the patient's condition, and this will not reveal the group allocations in other enrolled patients.

Data collection and management

During the study, all the participants' information will be gained by the study form which will be fulfilled by the investigator before the surgery. Outcomes include primary and secondary outcomes will be followed up by at least one investigator of the study team.

All the data will be recorded in the case report form (CRF) and synchronously input into the electronic CRF. Personal information of participants will be kept confidentially, and all data will be identified by a name acronym and a study identification number in the CRF. The Paper data will be preserved in a locked cabinet. All of the research data will be securely entered and filed in a designed Microsoft database for a minimum of 10 years after completion of the study. Only investigators of this study will have access to these data.

Statistical methods

Continuous variables will be presented as mean and standard deviation (SD) or median and inter-quartile range (IQR) as appropriate. The categorical data will be described as frequency, constituent ratio or percentage. One-way ANOVA and repeated measures ANOVA will be used to compare the changes of continuous variables among the three groups before and after treatment; Chi-square test will be used to compare the difference between groups. The severity of postanaesthetic shivering, pain scores and sedation scores will be compared by using Wilcoxon Rank Sum test. Statistical analyses

will be performed using SPSS V.17.0 (Chicago, Illinois, USA). $P < 0.05$ was considered statistically significant.

Ethics and dissemination

This study protocol has been approved by the ethics committee of The First Affiliated Hospital of Shandong First Medical University (YXLL-KY-2021(002)) and registered at ClinicalTrials.gov. The results for this trial will be presented at national and international scientific meetings or conferences and published in peer-reviewed international scientific journals.

Discussion

This single-centre, randomised, placebo-controlled, double-blinded trial is designed to investigate the effectiveness and safety of dexmedetomidine for the prevention of postoperative shivering in patients undergo elective CABG, and to compare the effectiveness of dexmedetomidine and meperidine on the incidence of shivering in patients undergo CABG. In the present study, all enrolled patients will be admitted to the ICU for postoperative care. Postoperative shivering will be evaluated according to 4 points scale of Wrench.[10]

This study has several strengths. This study is a well-designed single-centre, randomised, placebo-controlled and double-blinded trial with large sample size. To our knowledge, this is the new study to evaluate the impact of dexmedetomidine on shivering in patients undergo CABG. The incidence of shivering is usually high in the early recovery period of patients following cardiac surgery, especially in off-pump CABG.[20] Thus, the incidence and severity assessment of shivering is performed in the afternoon on the first day after the surgery. In addition, both dexmedetomidine and meperidine are effective in preventing postoperative shivering, and will not have influence on patients' prognosis. However, there are also several limitations in our study. For example, there might be some hemodynamic effects of dexmedetomidine, such as bradycardia and hypotension.[21]

Although there is an increasing number of randomised controlled studies regarding the prevention and treatment of postoperative shivering, the evidence of the effect on dexmedetomidine in patients undergo elective CABG surgery is still sparse. The potential significance of this study is that it may improve the effect of preventing postoperative shivering in patients undergo elective CABG surgery, which can enhance the recovery of patients after surgery and reduce the hospitalization time of patients.

Acknowledgements The authors thank all the contributors and collaborators for their support in this study. The authors also thank all the participating patients.

Author Contributions ML planned the study. ML and C-pG designed the statistical method. The work of patient recruitment and data collecting will be done by C-cC and JY. The study drugs were prepared by C-sW. C-cC and ML drafted the protocol. Y-lW and C-pG is the principal investigator of this study. All authors have read the manuscript and approved the final protocol.

Funding This work was supported by the National Natural Science Foundation of China (81770076, 82070078), and the Key Program of Natural Science Foundation of Shandong Province (ZR202010290035), and Academic Promotion Programme of Shandong First Medical University (2019QL015, 2019RC012), and Distinguished Taishan Scholars (ts20190981), and Young Taishan Scholars (tsqn201812144).

Competing interests None declared.

Patient consent for publication Not required.

Patient and public involvement There were no patients and public involved in the recruitment to and conduct of the study design and the outcome measures**.**

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Not applicable.

Abbreviation CABG, coronary artery bypass graft; ASA, American Society of Anaesthesiologists'; ICU, intensive care unit; PONV, postoperative nausea and vomiting; ECG, electrocardiography; NIBP, non-invasive blood pressure; SPO2, oxygen saturation; PCIA, Patient-controlled intravenous analgesia; CRF, case report form.

word count 2641

REFERENCES

1 Crossley AW. Peri-operative shivering. *Anaesthesia* 1992; 47: 193-5.
2 Insler SR, O'connor MS, Leventhal MJ, et al. Association between postoperative hypothermia and adverse outcome after coronary artery bypass surgery. *Ann Thorac Surg* 2000; 70: 175-81.
3 Dal D, Kose A, Honca M, et al. Efficacy of prophylactic ketamine in preventing postoperative shivering. *Br J Anaesth* 2005; 95: 189-92.
4 Botros JM, Mahmoud AMS, Ragab SG, et al. Comparative study between Dexmedetomidine and Ondansteron for prevention of post spinal shivering. A

randomized controlled trial. *BMC Anesthesiol* 2018; 18: 179.

5 Lopez MB. Postanaesthetic shivering - from pathophysiology to prevention. *Rom J Anaesth Intensive Care* 2018; 25: 73-81.

6 Lv M, Wang X, Qu W, et al. Nefopam for the prevention of perioperative shivering: a meta-analysis of randomized controlled trials. *BMC Anesthesiol* 2015; 15: 87.

7 Mohta M, Kumari N, Tyagi A, et al. Tramadol for prevention of postanaesthetic shivering: a randomised double-blind comparison with pethidine. *Anaesthesia* 2009; 64: 141-6.

8 Vanderstappen I, Vandermeersch E, Vanacker B, et al. The effect of prophylactic clonidine on postoperative shivering. A large prospective double-blind study. *Anaesthesia* 1996; 51: 351-5.

9 Dabir S, Jahandideh M, Abbasinazari M, et al. The efficacy of a single dose of pethidine, fentanyl and morphine in treating postanesthesia shivering. *Pak J Pharm Sci* 2011; 24: 513-7.

10 Wrench IJ, Singh P, Dennis AR, et al. The minimum effective doses of pethidine and doxapram in the treatment of post-anaesthetic shivering. *Anaesthesia* 1997; 52: 32-6.

11 Sun J, Zheng Z, Li YL, et al. Nalbuphine versus dexmedetomidine for treatment of combined spinal-epidural post-anesthetic shivering in pregnant women undergoing cesarean section. *J Int Med Res* 2019; 47: 4442-53.

12 Hoffman J, Hamner C. Effectiveness of dexmedetomidine use in general anesthesia to prevent postoperative shivering: a systematic review. *JBI database of systematic reviews and implementation reports* 2016; 13: 287-313.

13 Bicer C, Esmaoglu A, Akin A, et al. Dexmedetomidine and meperidine prevent postanaesthetic shivering. *Eur J Anaesthesiol* 2006; 23: 149-53.

14 Liu ZX, Xu FY, Liang X, et al. Efficacy of dexmedetomidine on postoperative shivering: a meta-analysis of clinical trials. *Can J Anaesth* 2015; 62: 816-29.

15 Wrench IJ, Cavill G, Ward JE, et al. Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering. *Br J Anaesth* 1997; 79: 541-2.

16 Lin YC, Chen CY, Liao YM, et al. Preventing shivering with adjuvant low dose intrathecal meperidine: A meta-analysis of randomized controlled trials with trial sequential analysis. *Scientific reports* 2017; 7: 15323.

17 Ayatollahi V, Hajiesmaeili MR, Behdad S, et al. Comparison of prophylactic use of meperidine and two low doses of ketamine for prevention of post-anesthetic shivering: A randomized double-blind placebo controlled trial. *J Res Med Sci* 2011; 16: 1340-6.

18 Porzio G, Aielli F, Verna L, et al. Efficacy and safety of deep, continuous palliative sedation at home: a retrospective, single-institution study. *Support Care Cancer* 2010; 18: 77-81.

19 Asl ME, Isazadefar K, Mohammadian A, et al. Ondansetron and meperidine prevent postoperative shivering after general anesthesia. *Middle East J Anaesthesiol* 2011; 21: 67-70.

20 Cruise C, Mackinnon J, Tough J, et al. Comparison of meperidine and pancuronium for the treatment of shivering after cardiac surgery. *Can J Anaesth* 1992; 39: 563-8.

21 Piao G, Wu J. Systematic assessment of dexmedetomidine as an anesthetic agent: a meta-analysis of randomized controlled trials. *Archives of medical science : AMS* 2014; 10: 19-24.

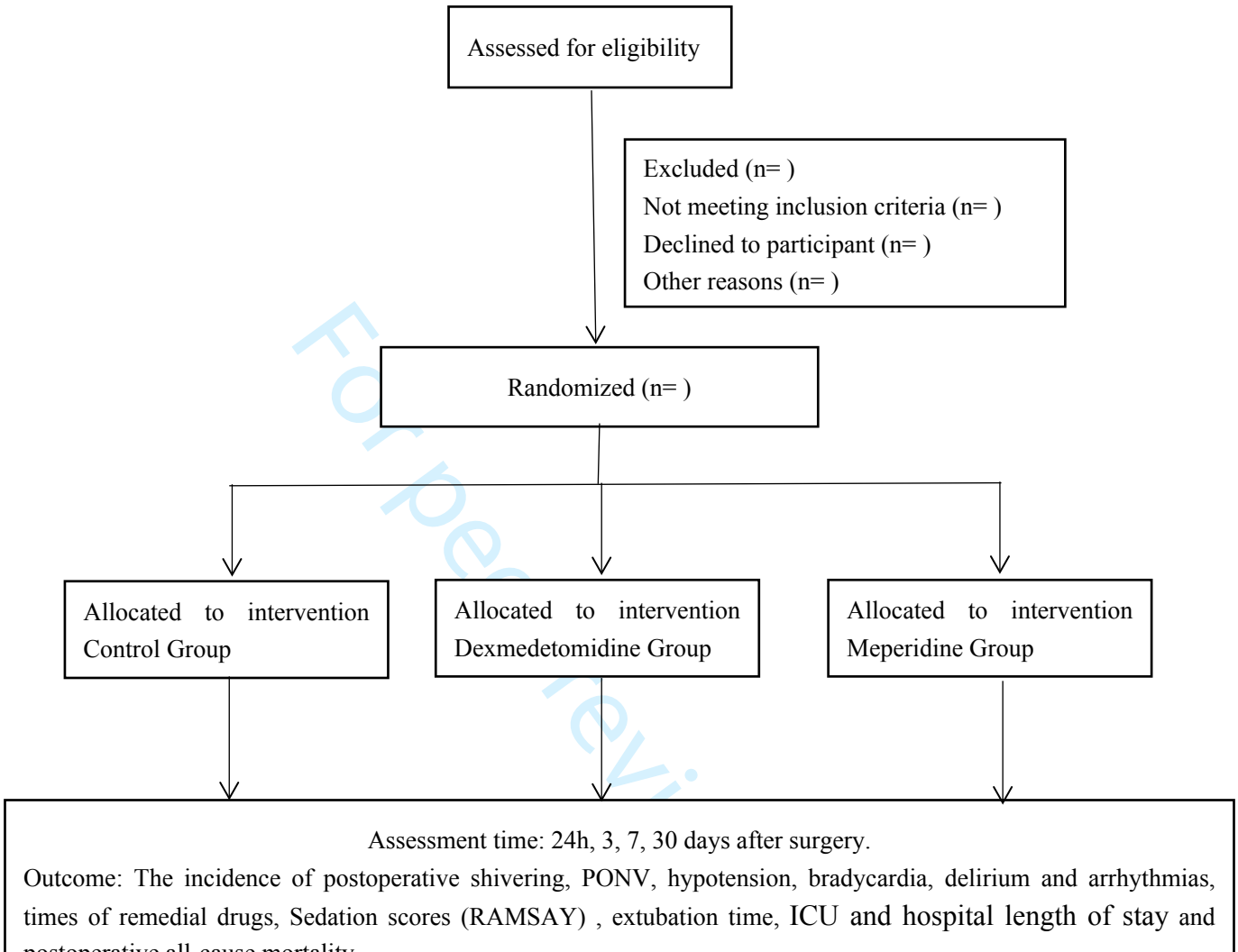


Figure 1 Consolidated Standards of Reporting Trials flow diagram. PONV, postoperative nausea and vomiting; ICU, intensive care unit.

		STUDY PERIOD								
	Enrolment	**Allocation**	**Post-allocation**						**Close-out**	
TIMEPOINT	**$-t_1$**	**0**	**t_1**	**t_2**	**t_3**	**t_4**	**t_5**	**t_6**	**After end of participation**	
ENROLMENT:										
Eligibility screen	×									
Informed consent	×									
Allocation		×								
INTERVENTIONS:										
group Dex			⟷							
group M			×							
group P										
ASSESSMENTS:										
Incidence of shivering					×					
Times of postoperative rescue drugs used					×					
Incidence of hypotension and bradycardia					×					
Sedation scores（RAMSAY）						×				
Incidence of delirium							×			
Incidence of arrhythmias					×					
Incidence of PONV						×				
ICU and hospital length of stay								×		
Postoperative all-cause mortality								×		

Figure 2 Standard Protocol Items: Recommendations for Interventional Trials.
-t_1, the day before surgery; 0, day of surgery; t_1, 30 minutes before the end of surgery; t_2, 15 minutes after study drugs administration; t_3, within postoperative 24 hours; t_4, within postoperative 3 days; t_5, within postoperative 7 days; t_6, within postoperative 30 days.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	10
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	9-10

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9-10
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2-3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3-4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be	4

		obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5-6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the	8

		protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8-9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-
Auditing	#23	Frequency and procedures for auditing trial conduct, if	n/a

		any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	-

authorship		professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Comparison of dexmedetomidine and meperidine for the prevention of shivering following coronary artery bypass graft: study protocol of a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-053865.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Nov-2021
Complete List of Authors:	Cao, Cuicui; Shandong First Medical University; The First Affiliated Hospital of Shandong First Medical University Lv, Meng; First Affiliated Hospital of Shandong First Medical University, Department of Anesthesiology Wei, Chuan; First Affiliated Hospital of Shandong First Medical University, Department of Anesthesiology Yan, Jie; Shandong First Medical University; The First Affiliated Hospital of Shandong First Medical University Gu, Chang; First Affiliated Hospital of Shandong First Medical University, Department of Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Surgery, Pharmacology and therapeutics
Keywords:	Anaesthesia in cardiology < ANAESTHETICS, Coronary heart disease < CARDIOLOGY, Cardiac surgery < SURGERY, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

Comparison of dexmedetomidine and meperidine for the prevention of shivering following coronary artery bypass graft: study protocol of a randomized controlled trial

Cui-cui Cao[1,2#], Meng Lv[2#], Chuan-song Wei[2], Jie Yan[1,2], Chang-ping Gu[2,3,4*]
[#]Co-First author
1 Shandong First Medical University & Shandong Academy of Medical Sciences
2 Department of Anesthesiology and Perioperative Medicine, The First Affiliated Hospital of Shandong First Medical University
3 Shandong Provincial Qianfoshan Hospital, Shandong Institute of Anesthesia and Respiratory Critical Medicine, Jinan, China
4 Department of Anesthesiology and Perioperative Medicine, Shandong Provincial Qianfoshan Hospital, Shandong University

cccbzyxy@163.com qylvmeng@163.com song6798@126.com

yj17ylh@163.com changpinggu@163.com

Corresponding author Chang-ping Gu, No.16766, Jingshi Road, Jinan, Shandong Province, China, changpinggu@163.com, 15806607957

ABSTRACT

Introduction: Shivering is a common complication in the postoperative period. The incidence of shivering has been reported to range from 5% to 65% under general anesthesia and as 33% during epidural anesthesia. Shivering can increase perioperative risk in patients. Both dexmedetomidine and meperidine are effective agents for the prevention of postanesthetic shivering. However, few studies have compared the anti-shivering effects of different agents following coronary artery bypass graft (CABG). This study aims to compare the effects of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing CABG.

Methods and analysis: A total of 180 patients aged 18 to 75 years, with an American Society of Anesthesiologists (ASA) grade of II-IV, undergoing elective CABG will be enrolled and randomly assigned to the dexmedetomidine, meperidine, and control groups (placebo) in an intended 1:1:1 allocation ratio. The patients will be followed up for 7 days after surgery. The primary outcome is the incidence of shivering within 24 h postoperatively. The secondary outcomes are the number of remedial drugs used after surgery, the incidence of postoperative hypotension and bradycardia, sedation scores,

endotracheal extubation time, intensive care unit (ICU) length of stay, incidence of postoperative delirium within 7 days after surgery, incidence of postoperative arrhythmias, incidence of postoperative nausea and vomiting (PONV), average hospital length of stay, and mortality rate 30 days after surgery.

Ethics and dissemination: The study protocol was approved by the ethics committee of The First Affiliated Hospital of Shandong First Medical University on January 20, 2021 (YXLL-KY-2021(002)) and registered at ClinicalTrials.gov. The results of this study will be presented at national and international scientific meetings and conferences. We plan to publish the data in peer-reviewed international scientific journals.

ARTICLE SUMMARY

Strengths and limitations of this study

1. The intervention is double-blinded.
2. This is a well-designed randomized controlled trial to compare the effectiveness of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing CABG.
3. The double-blinded and placebo-control design will enhance objectivity and help reduce bias.
4. This is a single-center clinical study.
5. Only early outcomes will be assessed including the incidence of shivering and other endpoints up to 30 days after the operation.

INTRODUCTION

Shivering is a common complication in patients during the postoperative period, with a reported incidence ranging from 5% to 65% in general anesthesia and 33% in epidural anesthesia.[1] The most common causes of shivering are hypothermia, blood transfusion, and pain. Patients with hypothermia after coronary artery bypass graft (CABG) surgery (< 36 °C) usually have a higher mortality rate and prolonged length of hospital stay.[2]

Shivering can increase the perioperative risk, and especially the risk of myocardial ischemia, in patients with coronary artery disease due to increased oxygen consumption (by 100%–600%). Moreover, interference with electrocardiography (ECG) and blood pressure monitoring, increased intracranial and intraocular pressure, increased production of carbon dioxide, and circulating catecholamines are also known side effects.[3 4] Therefore, it is important to prevent shivering after CABG. The incidence of postoperative shivering is still high, although some non-pharmacological methods, such as heating blankets or warming the administered fluid, have been used postoperatively.[5] Some medical agents, such as nefopam, tramadol, meperidine, morphine, fentanyl, doxapram, ketamine, and nalbuphine, have been reported to be effective in preventing

postanesthetic shivering.[6-12] However, there are few studies on the pharmacological interventions used for preventing shivering after CABG.

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist with an eight-fold higher affinity for the α_2-adrenoceptor than clonidine, which can cause sedation, analgesia, anxiolysis, and attenuation of the neuroendocrine and hemodynamic responses to anesthesia and surgery.[13 14] It may also provide a deeper level of sedation, decrease the incidence of postoperative nausea and vomiting (PONV), and increase hemodynamic stability during a sudden increase in stress.[15] Previous studies have shown that dexmedetomidine can reduce the incidence of shivering after both spinal and general anesthesia.[15] Nevertheless, the effects of dexmedetomidine on the incidence of shivering have not been reported in patients after CABG.

Meperidine is a combination of μ- and κ-receptor agonists. It can prevent hypothermia with peripheral vasoconstriction and central vasodilatation. Numerous trials have confirmed that meperidine is effectively used for the prevention and treatment of perioperative shivering.[16 17] Meperidine has some side effects such as nausea, vomiting, and respiratory depression, especially in patients who have previously used opioids or anesthetics and experienced hallucinations.[18] Therefore, it is important to find an effective agent therapy for preventing postoperative shivering with fewer side effects in patients undergoing CABG.

The aim of this study is to compare the effects of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing CABG.

METHODS AND ANALYSIS

Study design:

This study is a prospective, single-center, non-inferiority, double-blinded, randomized, placebo-controlled trial with three parallel arms. (Figure 1) It is designed to allocate patients in an intended 1:1:1 allocation ratio to compare the effectiveness of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing off-pump CABG.

This study protocol is written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT); the SPIRIT 2013 checklist has been included in Online Additional File 1.

Study setting

This study will be performed at the First Affiliated Hospital of Shandong First Medical University.

Participants

Inclusion criteria

Participants with the following criteria are eligible for inclusion in the study: (1) aged between 18 and 75 years, (2) undergoing elective CABG, (3) ASA grade of II–IV, and (4) in accordance with ethical guidelines, patients must voluntarily participate in the trial and sign the informed consent for the clinical study.

Exclusion criteria

Participants who meet one or more of the following criteria will be excluded from the study: (1) patients with neurological or psychiatric disorders, (2) hepatic and renal dysfunction, (3) severe hyperthyroidism or hypothyroidism, (4) a body temperature greater than 38 °C or less than 36 °C, (5) postoperative hemodynamic instability, (6) preoperative use of a left ventricular assistance device, (7) pa severe diabetic complications (diabetic ketoacidosis, hyperosmolar coma, various infections, diabetic nephropathy), (8) participation in other clinical studies within the past 3 months, (9) acute or chronic pain, (10) addiction to opioids, (11) drug abuse, (12) pain management, and (13) neuromuscular disease.

Intervention

A total of 180 patients will be randomly allocated to the dexmedetomidine group (group Dex, n=60), meperidine group (group M, n=60), and control group (group P, n=60). Standard monitoring, including ECG, non-invasive blood pressure (NIBP), and oxygen saturation (SPO_2) will be used in all patients, and radial artery catheterization and central venous catheterization will also be performed. The pulse rate, arterial blood pressure, peripheral arterial oxygen saturation, and nasopharyngeal temperature will be continuously monitored and recorded before study drug administration (baseline) and at 15, 30, 60, and 90 min after study drug administration. Neuromuscular block monitoring will occur intraoperatively using a peripheral nerve stimulator. The temperature of the operating room and ICU will be maintained at 22–25 °C.

None of the patients will receive medication prior to the induction of anesthesia. Anesthesia will be induced with midazolam (0.05 mg/kg), propofol (1–2 mg/kg), sufentanil (0.3 μg/kg), and atracurium (0.8 mg/kg) to facilitate tracheal intubation. Propofol and remifentanil will be continuously used during the surgery, and atracurium (0.4 mg/kg) will be added if required.

In the Dex group, the corresponding volume of saline will be administered to the patients intravenously for double-blind treatment, and the volume will be calculated according to the administration calculation method of meperidine (0.5 mg/kg). Then, dexmedetomidine (1 μg/kg) will be continuously infused over 15 min. In group M, meperidine (0.5 mg/kg) will be administered intravenously, and the same volume of saline will be continuously infused over 15 minutes. The volume will be calculated according to the administration calculation method of dexmedetomidine (1 μ g/kg). In group P (placebo), patients will receive the same volume of normal saline according to the administration calculation method of the Dex group or M group.

Dexmedetomidine, meperidine, and saline will be administered to the patients 30 min before the end of surgery. If the shivering score develops to more than 2, 20 mg of meperidine will be injected intravenously. Patient-controlled intravenous analgesia (PCIA) is used for postoperative analgesia. Sufentanil, ondansetron, dezocine, and saline will be added to the PCA pump to a total of 100 ml (the dose of all the analgesia agents used is according to the patient's age and body weight). The PCIA will be set at an infusion rate of 2 ml/h, including a bolus dose of 0.5 ml with a lock-out interval of 15 min. The PCIA will be used immediately after the operation to 48 h before tracheal extubation. No reversal agents will be administered. All patients will be transferred to

the ICU immediately after surgery. Tracheal extubation will be performed in the ICU after professional evaluation when the patients recover from anesthesia.

Outcomes

Primary outcome:

The primary outcome of this study is the incidence of shivering within 24 h postoperatively.

Secondary Outcomes:

1. Times of remedial drugs used after surgery within postoperative 24 hours.
2. The incidence of postoperative hypotension and bradycardia within 24 h postoperatively. Hypotension is defined as blood pressure less than 20% of baseline or systolic blood pressure < 90 mmHg. Heart rates greater than 100 beats or less than 60 beats per minute are defined as tachycardia and bradycardia, respectively.
3. Sedation scores: The Ramsay Sedation Scale[19] will be used to assess the sedation score within 3 days after surgery.
4. Other adverse events: The incidence of postoperative arrhythmias within 24 hours postoperatively, the incidence and severity of PONV by postoperative day 3, and the incidence of delirium within postoperative day 7 will be evaluated.
5. Extubation time of the endotracheal tube after surgery, length of ICU stay, length of hospital stay, and postoperative all-cause mortality within 30 days will also be recorded.

Study Schedule

Patient enrollment began in July 2021. It is estimated that this trial will take 18 to 24 months to enroll 180 patients. The estimated study completion date is August 2022.

Participant timeline

Screening of eligible participants can be performed during the preoperative visit the day before surgery. All patients must have volunteered to participate in the study and provided informed consent. Randomization will be implemented shortly before surgery, and patients will be allocated to groups Dex, M, and P according to the random number table method. All patients will have undergone CABG surgery under combined intravenous-inhalation anesthesia. All study drugs will have been administered 30 min before the end of surgery. All patients will be transferred to the ICU after surgery. The patients will be visited daily on the first 7 postoperative days by an investigator. Each visit will be documented, which will consist of an assessment of shivering, rescue drugs used, hypotension and bradycardia, PONV, sedation scores, delirium, arrhythmias, length of ICU and hospital stay, and postoperative all-cause mortality within 30 days. (Figure 2)

Sample size

Regarding the sample size, we calculated statistical power prior to the study. We set the statistical power to 0.80 with a one-sided type I error of 0.05. Patients will be randomly assigned into group Dex, group M, and group P in 1:1:1 ratio. According to previous

studies, we assumed that the incidence of shivering in group Dex and group M was 23% and 46.48%, respectively.[20 21] Based on these parameters, we calculated the sample size of 55 patients per group. To compensate for potential dropouts or inadequate procedures, we assumed an attrition rate of 5% and determined that 60 patients will be required in each group, to make a total of 180 patients.

Recruitment

Participants who meet the inclusion criteria are currently recruited for the study. The purpose, procedures, and potential risks and benefits of this study will be described to each patient and written informed consent will be obtained. If the patient cannot provide consent, written informed consent will be obtained from their authorized representatives. The patient will be assured that they are free to decline consent without consequences, and they can withdraw consent at any time without affecting treatment.

Allocation and randomization

The participants will be randomly allocated to either group Dex, group M, or group P with a 1:1:1 allocation ratio. The random sequence will be conducted via a computer-generated random number list by an investigator not involved in participant registration and data collection. This allocation sequence will be packed within sealed opaque envelopes and will not be disclosed to ensure concealment until the completion of the trial.

According to the allocation sequence, a research assistant will prepare the study drugs and the following experiments will be conducted by a blinded investigator.

Blinding

Both the patients and the investigators who participate in the intervention, observation, and assessment of this research will be unaware of the study drug assignment and group allocation until the results are analyzed. All the study drugs will be administered with identical appearances and labels. During the study, group allocation could be unmasked to protect the patient's safety. We can implement urgent unmasking if considered necessary for the sake of the patient's condition, and this will not reveal the group allocations of the other enrolled patients.

Data collection and management

During the study, all participant information will be gained by the study form, which will be filled out by an investigator before the surgery. Outcomes, including primary and secondary outcomes, will be followed up by at least one investigator from the study team.

All the data will be recorded in the case report form (CRF) and synchronously input into the electronic CRF. Personal information of participants will be kept confidential, and all data will be identified by a name acronym and a study identification number in the CRF. The paper data will be preserved in a locked cabinet. All research data will be securely entered and filed in a designed Microsoft database for a minimum of 10 years

after completion of the study. Only the investigators in this study will have access to these data.

Statistical methods

Continuous variables will be presented as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical data will be described as frequencies, constituent ratios, or percentages. One-way ANOVA and repeated measures ANOVA will be used to compare the changes in continuous variables among the three groups before and after treatment, and the chi-squared test will be used to compare the differences between groups. The severity of postanesthetic shivering, pain scores, and sedation scores will be compared using the Wilcoxon rank sum test. Statistical analyses will be performed using SPSS 22.0, and statistical significance is set at $P < 0.05$.

Ethics and dissemination

The study protocol was approved by the ethics committee of The First Affiliated Hospital of Shandong First Medical University (YXLL-KY-2021(002)) and registered at ClinicalTrials.gov. The results of this trial will be presented at national and international scientific meetings or conferences and published in peer-reviewed international scientific journals.

Patient and public involvement

There were no patients nor members of the public involved in recruitment or development of the study design and outcome measures**.**

DISCUSSION

This single-center, randomized, placebo-controlled, double-blinded trial was designed to compare the effectiveness of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing off-pump CABG. Postoperative shivering will be evaluated according to the 4-point Wrench scale.[22]

This study has several strengths. It is a well-designed, single-center, randomized, placebo-controlled, double-blinded trial with a large sample size. To our knowledge, this is the first study to evaluate the impact of dexmedetomidine on shivering in patients undergoing CABG. The incidence of shivering is usually high in the early recovery period of patients following cardiac surgery, especially in off-pump CABG.[23] Thus, the incidence and severity assessment of shivering is performed in the afternoon on the first day after the surgery. In addition, both dexmedetomidine and meperidine are effective in preventing postoperative shivering and do not influence patient prognosis. However, our study has several limitations. For example, there might be some hemodynamic effects of dexmedetomidine, such as bradycardia and hypotension.[24]

Acknowledgements The authors thank all the contributors and collaborators for their support in this study. The authors also thank all the participating patients.

Author Contributions ML planned the study. ML and C-pG designed the statistical method. The work of patient recruitment and data collecting will be done by C-cC and JY. The study drugs were prepared by C-sW. C-cC and ML drafted the protocol. C-pG is the principal investigator of this study. All authors have read the manuscript and approved the final protocol.

Funding This work was supported by the National Natural Science Foundation of China (82070078), and the Key Program of Natural Science Foundation of Shandong Province (ZR202010290035), and Academic Promotion Programme of Shandong First Medical University (2019QL015, 2019RC012), and Distinguished Taishan Scholars (ts20190981), and Young Taishan Scholars (tsqn201812144).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Not applicable.

Abbreviation CABG, coronary artery bypass graft; ASA, American Society of Anaesthesiologists'; ICU, intensive care unit; PONV, postoperative nausea and vomiting; ECG, electrocardiography; NIBP, non-invasive blood pressure; SPO_2, oxygen saturation; PCIA, Patient-controlled intravenous analgesia; CRF, case report form.

Figure caption:

Figure 1 Consolidated Standards of Reporting Trials flow diagram. PONV, postoperative nausea and vomiting; ICU, intensive care unit.

Figure 2 Standard Protocol Items: Recommendations for Interventional Trials.

-t1, the day before surgery; 0, day of surgery; t1, 30 minutes before the end of surgery; t2, 15 minutes after study drug administration; t3, within postoperative 24 hours; t4, within postoperative 3 days; t5, within postoperative 7 days; t6, within postoperative 30 days.

word count 2628

REFERENCES

1 Ameta N, Jacob M, Hasnain S, et al. Comparison of prophylactic use of ketamine, tramadol, and dexmedetomidine for prevention of shivering after spinal anesthesia. *J Anaesthesiol Clin Pharmacol* 2018; 34: 352-6.

2 Yu PJ, Cassiere HA, Kohn N, et al. Impact of Postoperative Hypothermia on Outcomes in Coronary Artery Bypass Surgery Patients. *J Cardiothorac Vasc Anesth* 2017; 31: 1257-61.

3 Dal D, Kose A, Honca M, et al. Efficacy of prophylactic ketamine in preventing postoperative shivering. *Br J Anaesth* 2005; 95: 189-92.

4 Botros JM, Mahmoud AMS, Ragab SG, et al. Comparative study between Dexmedetomidine and Ondansteron for prevention of post spinal shivering. A randomized controlled trial. *BMC Anesthesiol* 2018; 18: 179.

5 Lopez MB. Postanaesthetic shivering - from pathophysiology to prevention. *Rom J Anaesth Intensive Care* 2018; 25: 73-81.

6 Li S, Li P, Lin X. Efficacy of the prophylactic administration of tramadol against postoperative shivering: a meta-analysis of randomized controlled trials. Minerva Anestesiol 2017; 83: 79-87.

7 Lv M, Wang X, Qu W, et al. Nefopam for the prevention of perioperative shivering: a meta-analysis of randomized controlled trials. *BMC Anesthesiol* 2015; 15: 87.

8 Mohta M, Kumari N, Tyagi A, et al. Tramadol for prevention of postanaesthetic shivering: a randomised double-blind comparison with pethidine. *Anaesthesia* 2009; 64: 141-6.

9 Dabir S, Jahandideh M, Abbasinazari M, et al. The efficacy of a single dose of pethidine, fentanyl and morphine in treating postanesthesia shivering. *Pak J Pharm Sci* 2011; 24: 513-7.

10 Sun J, Zheng Z, Li YL, et al. Nalbuphine versus dexmedetomidine for treatment of combined spinal-epidural post-anesthetic shivering in pregnant women undergoing cesarean section. *J Int Med Res* 2019; 47: 4442-53.

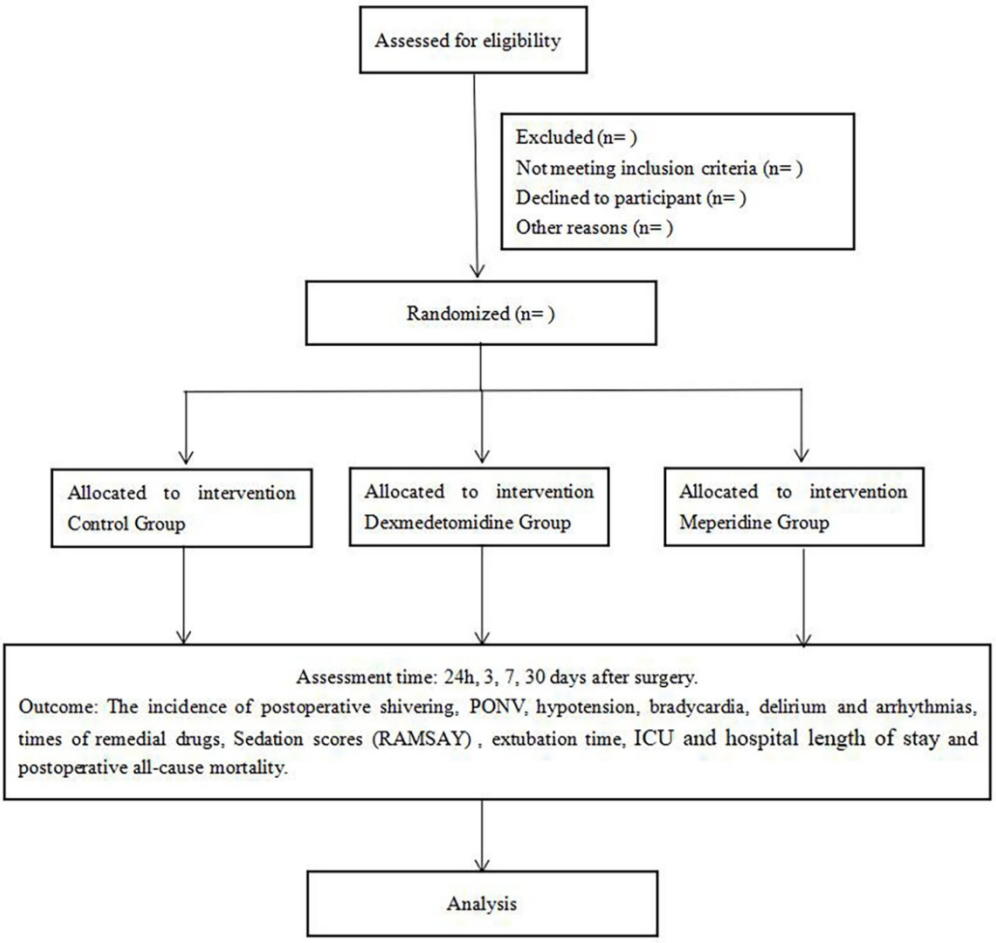
11 Hasannasab B, Banihashem N, Khoshbakht A. Prophylactic Effects of Doxapram, Ketamine and Meperidine in Postoperative Shivering. *Anesth Pain Med* 2016; 6: e27515.

12 Samimi Sadeh S, Hashemi E, Aminnejad R, et al. The Impact of Optimal Dose of Ketamine on Shivering Following Elective Abdominal Hysterectomy: A Randomised Comparative Study. *Anesth Pain Med* 2020; 10: e106220.

13 Hoffman J, Hamner C. Effectiveness of dexmedetomidine use in general anesthesia to prevent postoperative shivering: a systematic review. *JBI database of systematic reviews and implementation reports* 2016; 13: 287-313.

14 Wang N, Wang Z, Song X, et al. Intravenous dexmedetomidine versus intravenous clonidine for post spinal anesthesia shivering: a meta-analysis of randomized controlled trials. *Scott Med J* 2020; 65: 94-102.

15 Liu ZX, Xu FY, Liang X, et al. Efficacy of dexmedetomidine on postoperative shivering: a meta-analysis of clinical trials. *Can J Anaesth* 2015; 62: 816-29.
16 Lin YC, Chen CY, Liao YM, et al. Preventing shivering with adjuvant low dose intrathecal meperidine: A meta-analysis of randomized controlled trials with trial sequential analysis. *Scientific reports* 2017; 7: 15323.
17 Jayaraj A, Balachander H, Kuppusamy SK, et al. Comparison of meperidine, tramadol and fentanyl for post-spinal shivering prevention during cesarean delivery: A double-blind randomized controlled trial. *J Obstet Gynaecol Res* 2019; 45: 2202-8.
18 Ayatollahi V, Hajiesmaeili MR, Behdad S, et al. Comparison of prophylactic use of meperidine and two low doses of ketamine for prevention of post-anesthetic shivering: A randomized double-blind placebo controlled trial. *J Res Med Sci* 2011; 16: 1340-6.
19 Porzio G, Aielli F, Verna L, et al. Efficacy and safety of deep, continuous palliative sedation at home: a retrospective, single-institution study. *Support Care Cancer* 2010; 18: 77-81.
20 Bicer C, Esmaoglu A, Akin A, et al. Dexmedetomidine and meperidine prevent postanaesthetic shivering. *Eur J Anaesthesiol* 2006; 23: 149-53.
21 Asl ME, Isazadefar K, Mohammadian A, et al. Ondansetron and meperidine prevent postoperative shivering after general anesthesia. *Middle East J Anaesthesiol* 2011; 21: 67-70.
22 Gecaj-Gashi A, Hashimi M, Sada F, et al. Prophylactic ketamine reduces incidence of postanaesthetic shivering. *Niger J Med* 2010; 19: 267-70.
23 Cruise C, Mackinnon J, Tough J, et al. Comparison of meperidine and pancuronium for the treatment of shivering after cardiac surgery. *Can J Anaesth* 1992; 39: 563-8.
24 Piao G, Wu J. Systematic assessment of dexmedetomidine as an anesthetic agent: a meta-analysis of randomized controlled trials. *Archives of medical science : AMS* 2014; 10: 19-24.



99x94mm (300 x 300 DPI)

		STUDY PERIOD								
	Enrolment	Allocation	Post-allocation						Close-out	
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	After end of participation	
ENROLLMENT:										
Eligibility screen	×									
Informed consent	×									
Allocation		×								
INTERVENTIONS:										
Group Dex			←	→						
Group M			×							
Group P										
ASSESSMENTS:										
Incidence of shivering					×					
Number of times postoperative rescue drugs used					×					
Incidence of hypotension and bradycardia					×					
Sedation scores (RAMSAY)						×				
Incidence of delirium							×			
Incidence of arrhythmias					×					
Incidence of PONV						×				
ICU and hospital length of stay								×		
Postoperative all-cause mortality								×		

94x159mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	8

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be	3

		obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	3-4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4-5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the	6-7

		protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6-7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-
Auditing	#23	Frequency and procedures for auditing trial conduct, if	n/a

		any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6-7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	-

authorship		professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Comparison of dexmedetomidine and meperidine for the prevention of shivering following coronary artery bypass graft: study protocol of a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-053865.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Dec-2021
Complete List of Authors:	Cao, Cuicui; Shandong First Medical University; The First Affiliated Hospital of Shandong First Medical University Lv, Meng; First Affiliated Hospital of Shandong First Medical University, Department of Anesthesiology Wei, Chuan; First Affiliated Hospital of Shandong First Medical University, Department of Anesthesiology Yan, Jie; Shandong First Medical University; The First Affiliated Hospital of Shandong First Medical University Gu, Chang; First Affiliated Hospital of Shandong First Medical University, Department of Anesthesiology Wang, Yue; First Affiliated Hospital of Shandong First Medical University, Department of Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Surgery, Pharmacology and therapeutics
Keywords:	Anaesthesia in cardiology < ANAESTHETICS, Coronary heart disease < CARDIOLOGY, Cardiac surgery < SURGERY, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

Comparison of dexmedetomidine and meperidine for the prevention of shivering following coronary artery bypass graft: study protocol of a randomized controlled trial

Cui-cui Cao[1,2#], Meng Lv[2#], Chuan-song Wei[2], Jie Yan[1,2], Chang-ping Gu[2,3,4*], Yue-lan Wang[2,3,4]

[#]Co-First author

1 Shandong First Medical University & Shandong Academy of Medical Sciences

2 Department of Anesthesiology and Perioperative Medicine, The First Affiliated Hospital of Shandong First Medical University

3 Shandong Provincial Qianfoshan Hospital, Shandong Institute of Anesthesia and Respiratory Critical Medicine, Jinan, China

4 Department of Anesthesiology and Perioperative Medicine, Shandong Provincial Qianfoshan Hospital, Shandong University

cccbzyxy@163.com qylvmeng@163.com song6798@126.com

yj17ylh@163.com changpinggu@163.com wyldgf@163.com

Corresponding author Chang-ping Gu, No.16766, Jingshi Road, Jinan, Shandong Province, China, changpinggu@163.com, 15806607957

ABSTRACT

Introduction: Shivering is a common complication in the postoperative period. The incidence of shivering has been reported to range from 5% to 65% under general anesthesia and as 33% during epidural anesthesia. Shivering can increase perioperative risk in patients. Both dexmedetomidine and meperidine are effective agents for the prevention of postanesthetic shivering. However, few studies have compared the anti-shivering effects of different agents following coronary artery bypass graft (CABG). This study aims to compare the effects of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing CABG.

Methods and analysis: A total of 180 patients aged 18 to 75 years, with an American Society of Anesthesiologists (ASA) grade of II-IV, undergoing elective CABG will be enrolled and randomly assigned to the dexmedetomidine, meperidine, and control groups (placebo) in an intended 1:1:1 allocation ratio. The patients will be followed up for 7 days after surgery. The primary outcome is the incidence of shivering within 24 h postoperatively. The secondary outcomes are the number of remedial drugs used after

surgery, the incidence of postoperative hypotension and bradycardia, sedation scores, endotracheal extubation time, intensive care unit (ICU) length of stay, incidence of postoperative delirium within 7 days after surgery, incidence of postoperative arrhythmias, incidence of postoperative nausea and vomiting (PONV), average hospital length of stay, and mortality rate 30 days after surgery.

Ethics and dissemination: The study protocol was approved by the ethics committee of The First Affiliated Hospital of Shandong First Medical University on January 20, 2021 (YXLL-KY-2021(002)) and registered at ClinicalTrials.gov. The results of this study will be presented at national and international scientific meetings and conferences. We plan to publish the data in peer-reviewed international scientific journals.

ARTICLE SUMMARY

Strengths and limitations of this study

1. This is a well-designed randomized controlled trial for the prevention of postoperative shivering after coronary artery bypass graft.
2. The double-blinded and placebo-control design will enhance objectivity and help reduce bias.
3. This is a three groups, non-inferiority, randomized controlled trial, which is the most efficient.
4. This is a single center study, thus the external generality is limited.

INTRODUCTION

Shivering is a common complication in patients during the postoperative period, with a reported incidence ranging from 5% to 65% in general anesthesia and 33% in epidural anesthesia.[1] The most common causes of shivering are hypothermia, blood transfusion, and pain. Patients with hypothermia after coronary artery bypass graft (CABG) surgery (< 36 °C) usually have a higher mortality rate and prolonged length of hospital stay.[2]

Shivering can increase the perioperative risk, and especially the risk of myocardial ischemia, in patients with coronary artery disease due to increased oxygen consumption (by 100%–600%). Moreover, interference with electrocardiography (ECG) and blood pressure monitoring, increased intracranial and intraocular pressure, increased production of carbon dioxide, and circulating catecholamines are also known side effects.[3 4] Therefore, it is important to prevent shivering after CABG. The incidence of postoperative shivering is still high, although some non-pharmacological methods, such as heating blankets or warming the administered fluid, have been used postoperatively.[5] Some medical agents, such as nefopam, tramadol, meperidine, morphine, fentanyl, doxapram, ketamine, and nalbuphine, have been reported to be effective in preventing postanesthetic shivering.[6-12] However, there are few studies on the pharmacological interventions used for preventing shivering after CABG.

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist with an eight-fold higher affinity for the α_2-adrenoceptor than clonidine, which can cause sedation,

analgesia, anxiolysis, and attenuation of the neuroendocrine and hemodynamic responses to anesthesia and surgery.[13 14] It may also provide a deeper level of sedation, decrease the incidence of postoperative nausea and vomiting (PONV), and increase hemodynamic stability during a sudden increase in stress.[15] Previous studies have shown that dexmedetomidine can reduce the incidence of shivering after both spinal and general anesthesia.[15] Nevertheless, the effects of dexmedetomidine on the incidence of shivering have not been reported in patients after CABG.

Meperidine is a combination of μ- and κ-receptor agonists. It can prevent hypothermia with peripheral vasoconstriction and central vasodilatation. Numerous trials have confirmed that meperidine is effectively used for the prevention and treatment of perioperative shivering.[16 17] Meperidine has some side effects such as nausea, vomiting, and respiratory depression, especially in patients who have previously used opioids or anesthetics and experienced hallucinations.[18] Therefore, it is important to find an effective agent therapy for preventing postoperative shivering with fewer side effects in patients undergoing CABG.

The aim of this study is to compare the effects of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing CABG.

METHODS AND ANALYSIS

Study design:

This study is a prospective, single-center, non-inferiority, double-blinded, randomized, placebo-controlled trial with three parallel arms. (Figure 1) It is designed to allocate patients in an intended 1:1:1 allocation ratio to compare the effectiveness of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing off-pump CABG.

This study protocol is written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT); the SPIRIT 2013 checklist has been included in Online Additional File 1.

Study setting

This study will be performed at the First Affiliated Hospital of Shandong First Medical University.

Participants

Inclusion criteria

Participants with the following criteria are eligible for inclusion in the study: (1) aged between 18 and 75 years, (2) undergoing elective CABG, (3) ASA grade of II–IV, and (4) in accordance with ethical guidelines, patients must voluntarily participate in the trial and sign the informed consent for the clinical study.

Exclusion criteria

Participants who meet one or more of the following criteria will be excluded from the study: (1) patients with neurological or psychiatric disorders, (2) hepatic and renal dysfunction, (3) severe hyperthyroidism or hypothyroidism, (4) a body temperature greater than 38 °C or less than 36 °C, (5) postoperative hemodynamic instability, (6)

preoperative use of a left ventricular assistance device, (7) pa severe diabetic complications (diabetic ketoacidosis, hyperosmolar coma, various infections, diabetic nephropathy), (8) participation in other clinical studies within the past 3 months, (9) acute or chronic pain, (10) addiction to opioids, (11) drug abuse, (12) pain management, and (13) neuromuscular disease, (14) on-pump CABG.

Intervention

A total of 180 patients will be randomly allocated to the dexmedetomidine group (group Dex, n=60), meperidine group (group M, n=60), and control group (group P, n=60). Standard monitoring, including ECG, non-invasive blood pressure (NIBP), and oxygen saturation (SPO_2) will be used in all patients, and radial artery catheterization and central venous catheterization will also be performed. The pulse rate, arterial blood pressure, peripheral arterial oxygen saturation, and nasopharyngeal temperature will be continuously monitored and recorded before study drug administration (baseline) and at 15, 30, 60, and 90 min after study drug administration. Neuromuscular block monitoring will occur intraoperatively using a peripheral nerve stimulator. The temperature of the operating room and ICU will be maintained at 22–25 °C.

None of the patients will receive medication prior to the induction of anesthesia. Anesthesia will be induced with midazolam (0.05 mg/kg), propofol (1–2 mg/kg), sufentanil (0.3 μg/kg), and atracurium (0.8 mg/kg) to facilitate tracheal intubation. Propofol and remifentanil will be continuously used during the surgery, and atracurium (0.4 mg/kg) will be added if required.

In the Dex group, the corresponding volume of saline will be administered to the patients intravenously for double-blind treatment, and the volume will be calculated according to the administration calculation method of meperidine (0.5 mg/kg). Then, dexmedetomidine (1 μg/kg) will be continuously infused over 15 min. In group M, meperidine (0.5 mg/kg) will be administered intravenously, and the same volume of saline will be continuously infused over 15 minutes. The volume will be calculated according to the administration calculation method of dexmedetomidine (1 μ g/kg). In group P (placebo), patients will receive the same volume of normal saline according to the administration calculation method of the Dex group or M group.

Dexmedetomidine, meperidine, and saline will be administered to the patients 30 min before the end of surgery. If the shivering score develops to more than 2, 20 mg of meperidine will be injected intravenously. Patient-controlled intravenous analgesia (PCIA) is used for postoperative analgesia. Sufentanil, ondansetron, dezocine, and saline will be added to the PCA pump to a total of 100 ml (the dose of all the analgesia agents used is according to the patient's age and body weight). The PCIA will be set at an infusion rate of 2 ml/h, including a bolus dose of 0.5 ml with a lock-out interval of 15 min. The PCIA will be used immediately after the operation to 48 h before tracheal extubation. No reversal agents will be administered. All patients will be transferred to the ICU immediately after surgery. Tracheal extubation will be performed in the ICU after professional evaluation when the patients recover from anesthesia.

Outcomes

Primary outcome:
The primary outcome of this study is the incidence of shivering within 24 h postoperatively.

Secondary Outcomes:
1. Times of remedial drugs used after surgery within postoperative 24 hours.
2. The incidence of postoperative hypotension and bradycardia within 24 h postoperatively. Hypotension is defined as blood pressure less than 20% of baseline or systolic blood pressure < 90 mmHg. Heart rates greater than 100 beats or less than 60 beats per minute are defined as tachycardia and bradycardia, respectively.
3. Sedation scores: The Ramsay Sedation Scale[19] will be used to assess the sedation score within 3 days after surgery.
4. Other adverse events: The incidence of postoperative arrhythmias within 24 hours postoperatively, the incidence and severity of PONV by postoperative day 3, and the incidence of delirium within postoperative day 7 will be evaluated.
5. Extubation time of the endotracheal tube after surgery, length of ICU stay, length of hospital stay, and postoperative all-cause mortality within 30 days will also be recorded.

Study Schedule
Patient enrollment began in July 2021. It is estimated that this trial will take 18 to 24 months to enroll 180 patients. The estimated study completion date is August 2022.

Participant timeline
Screening of eligible participants can be performed during the preoperative visit the day before surgery. All patients must have volunteered to participate in the study and provided informed consent. Randomization will be implemented shortly before surgery, and patients will be allocated to groups Dex, M, and P according to the random number table method. All patients will have undergone CABG surgery under combined intravenous-inhalation anesthesia. All study drugs will have been administered 30 min before the end of surgery. All patients will be transferred to the ICU after surgery. The patients will be visited daily on the first 7 postoperative days by an investigator. Each visit will be documented, which will consist of an assessment of shivering, rescue drugs used, hypotension and bradycardia, PONV, sedation scores, delirium, arrhythmias, length of ICU and hospital stay, and postoperative all-cause mortality within 30 days. (Figure 2)

Sample size
Regarding the sample size, we calculated statistical power prior to the study. We set the statistical power to 0.80 with a one-sided type I error of 0.05. Patients will be randomly assigned into group Dex, group M, and group P in 1:1:1 ratio. According to previous studies, we assumed that the incidence of shivering in group Dex and group M was 23% and 46.48%, respectively.[20 21] Based on these parameters, we calculated the sample size of 55 patients per group. To compensate for potential dropouts or inadequate procedures, we assumed an attrition rate of 5% and determined that 60 patients will be required in

each group, to make a total of 180 patients.

Recruitment

Participants who meet the inclusion criteria are currently recruited for the study. The purpose, procedures, and potential risks and benefits of this study will be described to each patient and written informed consent will be obtained. If the patient cannot provide consent, written informed consent will be obtained from their authorized representatives. The patient will be assured that they are free to decline consent without consequences, and they can withdraw consent at any time without affecting treatment.

Allocation and randomization

The participants will be randomly allocated to either group Dex, group M, or group P with a 1:1:1 allocation ratio. The random sequence will be conducted via a computer-generated random number list by an investigator not involved in participant registration and data collection. This allocation sequence will be packed within sealed opaque envelopes and will not be disclosed to ensure concealment until the completion of the trial.

According to the allocation sequence, a research assistant will prepare the study drugs and the following experiments will be conducted by a blinded investigator.

Blinding

Both the patients and the investigators who participate in the intervention, observation, and assessment of this research will be unaware of the study drug assignment and group allocation until the results are analyzed. All the study drugs will be administered with identical appearances and labels. During the study, group allocation could be unmasked to protect the patient's safety. We can implement urgent unmasking if considered necessary for the sake of the patient's condition, and this will not reveal the group allocations of the other enrolled patients.

Data collection and management

During the study, all participant information will be gained by the study form, which will be filled out by an investigator before the surgery. Outcomes, including primary and secondary outcomes, will be followed up by at least one investigator from the study team.

All the data will be recorded in the case report form (CRF) and synchronously input into the electronic CRF. Personal information of participants will be kept confidential, and all data will be identified by a name acronym and a study identification number in the CRF. The paper data will be preserved in a locked cabinet. All research data will be securely entered and filed in a designed Microsoft database for a minimum of 10 years after completion of the study. Only the investigators in this study will have access to these data.

Statistical methods

Continuous variables will be presented as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical data will be described as frequencies, constituent ratios, or percentages. One-way ANOVA and repeated measures ANOVA will be used to compare the changes in continuous variables among the three groups before and after treatment, and the chi-squared test will be used to compare the differences between groups. The severity of postanesthetic shivering, pain scores, and sedation scores will be compared using the Wilcoxon rank sum test. Statistical analyses will be performed using SPSS 22.0, and statistical significance is set at $P < 0.05$.

Ethics and dissemination

The study protocol was approved by the ethics committee of The First Affiliated Hospital of Shandong First Medical University (YXLL-KY-2021(002)) and registered at ClinicalTrials.gov. The results of this trial will be presented at national and international scientific meetings or conferences and published in peer-reviewed international scientific journals.

Patient and public involvement

There were no patients nor members of the public involved in recruitment or development of the study design and outcome measures**.**

DISCUSSION

This single-center, randomized, placebo-controlled, double-blinded trial was designed to compare the effectiveness of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing off-pump CABG. Postoperative shivering will be evaluated according to the 4-point Wrench scale.[22]

This study has several strengths. It is a well-designed, single-center, randomized, placebo-controlled, double-blinded trial with a large sample size. To our knowledge, this is the first study to evaluate the impact of dexmedetomidine on shivering in patients undergoing CABG. The incidence of shivering is usually high in the early recovery period of patients following cardiac surgery, especially in off-pump CABG.[23] Thus, the incidence and severity assessment of shivering is performed in the afternoon on the first day after the surgery. In addition, both dexmedetomidine and meperidine are effective in preventing postoperative shivering and do not influence patient prognosis. However, our study has several limitations. For example, there might be some hemodynamic effects of dexmedetomidine, such as bradycardia and hypotension.[24]

Acknowledgements The authors thank all the contributors and collaborators for their support in this study. The authors also thank all the participating patients.

Author Contributions ML and Y-lW planned the study. ML and C-pG designed the statistical method. The work of patient recruitment and data collecting will be done by C-cC and JY. The study drugs were prepared by C-sW. C-cC and ML drafted the protocol. C-pG is the principal investigator of this study. All authors have read the

manuscript and approved the final protocol.

Funding This work was supported by the National Natural Science Foundation of China (82070078), and the Key Program of Natural Science Foundation of Shandong Province (ZR202010290035), and Academic Promotion Programme of Shandong First Medical University (2019QL015, 2019RC012), and Distinguished Taishan Scholars (ts20190981), and Young Taishan Scholars (tsqn201812144).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Not applicable.

Abbreviation CABG, coronary artery bypass graft; ASA, American Society of Anaesthesiologists'; ICU, intensive care unit; PONV, postoperative nausea and vomiting; ECG, electrocardiography; NIBP, non-invasive blood pressure; SPO_2, oxygen saturation; PCIA, Patient-controlled intravenous analgesia; CRF, case report form.

Figure caption:

Figure 1 Consolidated Standards of Reporting Trials flow diagram. PONV, postoperative nausea and vomiting; ICU, intensive care unit.

Figure 2 Standard Protocol Items: Recommendations for Interventional Trials.

-t1, the day before surgery; 0, day of surgery; t1, 30 minutes before the end of surgery; t2, 15 minutes after study drug administration; t3, within postoperative 24 hours; t4, within postoperative 3 days; t5, within postoperative 7 days; t6, within postoperative 30 days.

word count 2633

REFERENCES

1 Ameta N, Jacob M, Hasnain S, et al. Comparison of prophylactic use of ketamine, tramadol, and dexmedetomidine for prevention of shivering after spinal anesthesia. *J Anaesthesiol Clin Pharmacol* 2018; 34: 352-6.

2 Yu PJ, Cassiere HA, Kohn N, et al. Impact of Postoperative Hypothermia on Outcomes in Coronary Artery Bypass Surgery Patients. *J Cardiothorac Vasc Anesth* 2017; 31: 1257-61.

3 Dal D, Kose A, Honca M, et al. Efficacy of prophylactic ketamine in preventing postoperative shivering. *Br J Anaesth* 2005; 95: 189-92.

4 Botros JM, Mahmoud AMS, Ragab SG, et al. Comparative study between Dexmedetomidine and Ondansteron for prevention of post spinal shivering. A randomized controlled trial. *BMC Anesthesiol* 2018; 18: 179.

5 Lopez MB. Postanaesthetic shivering - from pathophysiology to prevention. *Rom J Anaesth Intensive Care* 2018; 25: 73-81.

6 Li S, Li P, Lin X. Efficacy of the prophylactic administration of tramadol against postoperative shivering: a meta-analysis of randomized controlled trials. Minerva Anestesiol 2017; 83: 79-87.

7 Lv M, Wang X, Qu W, et al. Nefopam for the prevention of perioperative shivering: a meta-analysis of randomized controlled trials. *BMC Anesthesiol* 2015; 15: 87.

8 Mohta M, Kumari N, Tyagi A, et al. Tramadol for prevention of postanaesthetic shivering: a randomised double-blind comparison with pethidine. *Anaesthesia* 2009; 64: 141-6.

9 Dabir S, Jahandideh M, Abbasinazari M, et al. The efficacy of a single dose of pethidine, fentanyl and morphine in treating postanesthesia shivering. *Pak J Pharm Sci* 2011; 24: 513-7.

10 Sun J, Zheng Z, Li YL, et al. Nalbuphine versus dexmedetomidine for treatment of combined spinal-epidural post-anesthetic shivering in pregnant women undergoing cesarean section. *J Int Med Res* 2019; 47: 4442-53.

11 Hasannasab B, Banihashem N, Khoshbakht A. Prophylactic Effects of Doxapram, Ketamine and Meperidine in Postoperative Shivering. *Anesth Pain Med* 2016; 6: e27515.

12 Samimi Sadeh S, Hashemi E, Aminnejad R, et al. The Impact of Optimal Dose of Ketamine on Shivering Following Elective Abdominal Hysterectomy: A Randomised Comparative Study. *Anesth Pain Med* 2020; 10: e106220.

13 Hoffman J, Hamner C. Effectiveness of dexmedetomidine use in general anesthesia to prevent postoperative shivering: a systematic review. *JBI database of systematic reviews and implementation reports* 2016; 13: 287-313.

14 Wang N, Wang Z, Song X, et al. Intravenous dexmedetomidine versus intravenous clonidine for post spinal anesthesia shivering: a meta-analysis of randomized controlled trials. *Scott Med J* 2020; 65: 94-102.

15 Liu ZX, Xu FY, Liang X, et al. Efficacy of dexmedetomidine on postoperative shivering: a meta-analysis of clinical trials. *Can J Anaesth* 2015; 62: 816-29.

16 Lin YC, Chen CY, Liao YM, et al. Preventing shivering with adjuvant low dose intrathecal meperidine: A meta-analysis of randomized controlled trials with trial sequential analysis. *Scientific reports* 2017; 7: 15323.

17 Jayaraj A, Balachander H, Kuppusamy SK, et al. Comparison of meperidine, tramadol and fentanyl for post-spinal shivering prevention during cesarean delivery: A double-blind randomized controlled trial. *J Obstet Gynaecol Res* 2019; 45: 2202-8.

18 Ayatollahi V, Hajiesmaeili MR, Behdad S, et al. Comparison of prophylactic use of meperidine and two low doses of ketamine for prevention of post-anesthetic shivering: A randomized double-blind placebo controlled trial. *J Res Med Sci* 2011; 16: 1340-6.

19 Porzio G, Aielli F, Verna L, et al. Efficacy and safety of deep, continuous palliative sedation at home: a retrospective, single-institution study. *Support Care Cancer* 2010; 18: 77-81.

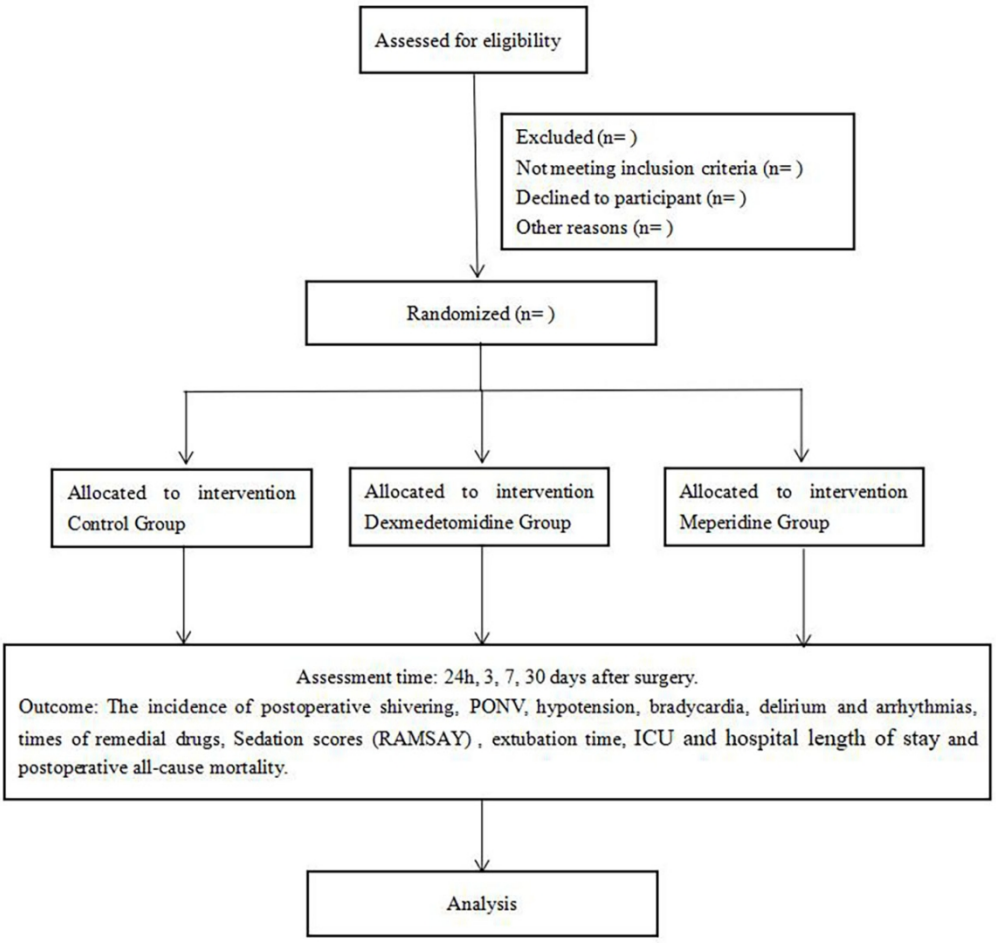
20 Bicer C, Esmaoglu A, Akin A, et al. Dexmedetomidine and meperidine prevent postanaesthetic shivering. *Eur J Anaesthesiol* 2006; 23: 149-53.

21 Asl ME, Isazadefar K, Mohammadian A, et al. Ondansetron and meperidine prevent postoperative shivering after general anesthesia. *Middle East J Anaesthesiol* 2011; 21: 67-70.

22 Gecaj-Gashi A, Hashimi M, Sada F, et al. Prophylactic ketamine reduces incidence of postanaesthetic shivering. *Niger J Med* 2010; 19: 267-70.

23 Cruise C, Mackinnon J, Tough J, et al. Comparison of meperidine and pancuronium for the treatment of shivering after cardiac surgery. *Can J Anaesth* 1992; 39: 563-8.

24 Piao G, Wu J. Systematic assessment of dexmedetomidine as an anesthetic agent: a meta-analysis of randomized controlled trials. *Archives of medical science : AMS* 2014; 10: 19-24.



100x94mm (320 x 320 DPI)

		STUDY PERIOD								
	Enrolment	Allocation	Post-allocation						Close-out	
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	After end of participation	
ENROLLMENT:										
Eligibility screen	×									
Informed consent	×									
Allocation		×								
INTERVENTIONS:										
Group Dex			⟷							
Group M			×							
Group P										
ASSESSMENTS:										
Incidence of shivering					×					
Times of remedial drugs used					×					
Incidence of hypotension and bradycardia					×					
Sedation scores (RAMSAY)						×				
Incidence of delirium							×			
Incidence of arrhythmias					×					
Incidence of PONV						×				
ICU and hospital length of stay								×		
Postoperative all-cause mortality								×		

94x158mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	8

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be	3

		obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	3-4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4-5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the	6-7

		protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6-7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	-
Auditing	#23	Frequency and procedures for auditing trial conduct, if	n/a

		any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6-7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	-

authorship		professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a