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

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

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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

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3 nausea and vomiting (PONV), the average hospital length of stay, and the mortality rate
4 30 days after the operation.

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

12
13 **Trial registration number** NCT04735965

14 **Keywords** Shivering dexmedetomidine meperidine CABG

15 16 17 **Article Summary**

18 19 **Strengths and limitations of this study**

- 20 1.The intervention is double-blinded.
 - 21 2.This is a well-designed randomised controlled trial to explore the effectiveness and
22 safety of dexmedetomidine for the prevention of postoperative shivering in patients
23 undergo elective CABG, and to compare the effectiveness of dexmedetomidine and
24 meperidine on the incidence of shivering in patients undergo CABG.
 - 25 3.The double-blinded and placebo-control design will enhance objectivity and help
26 reduce bias.
 - 27 4.This is a single-centre clinical study.
 - 28 5.Only early outcomes will be assessed including the incidence of shivering and other
29 endpoints up to 30 days after the operation.
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38 39 **INTRODUCTION**

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

45 Shivering can increase the perioperative risk of patients with coronary artery disease
46 due to the increased oxygen consumption (by 100–600%), especially the risk of
47 myocardial ischemia. Moreover, the interference with monitoring of
48 electrocardiography (ECG) and blood pressure, the increase of intracranial and
49 intraocular pressure, increased production of carbon dioxide and circulating
50 catecholamines are also the side effects.^{3,4} Therefore, it is important to prevent shivering
51 after CABG. The incidence of postoperative shivering is still high, although some non-
52 pharmacological methods such as heating blanket or warming the administered fluid
53 has been used after the surgery.⁵ Some medical agents such as nefopam, tramadol,
54 meperidine (pethidine), clonidine, morphine, fentanyl, doxapram, ketamine,
55 nalbuphine were reported effective in preventing postanesthetic shivering.^{3 6-11} But
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3 there are few studies of pharmacological interventions used for preventing shivering
4 after CABG.
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6 Dexmedetomidine is a highly selective α_2 -adrenoceptor agonist with an eight times
7 higher affinity for α_2 -adrenoceptor than clonidine which can cause sedation, analgesia,
8 anxiolysis and attenuation of the neuroendocrine and hemodynamic responses to
9 anesthesia and surgery.^{12 13} It may also provide a deeper level of sedation, decrease the
10 incidence of PONV, and increase hemodynamic stability during a sudden increase in
11 stress.¹⁴ Previous studies have shown that dexmedetomidine can reduce the incidence
12 of shivering after both spinal anesthesia and general anesthesia.¹⁴ But the effects of
13 dexmedetomidine on the incidence of shivering has not been reported in patients after
14 CABG.
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17 Meperidine is a combined μ - and κ - receptor agonist. And it stimulates μ receptors
18 to exert analgesic effect. It can prevent hypothermia with peripheral vasoconstriction
19 and central vasodilatation. Numerous trials have confirmed that meperidine was
20 effectively used for the prevention and treatment of perioperative shivering.^{15 16} But the
21 anti-shivering mechanism of meperidine is still unclear. And meperidine also has some
22 side effects such as nausea, vomiting, respiratory depression especially in patients who
23 had previously used opioid or anesthetics, and hallucination.¹⁷ Therefore, it is important
24 to find an effective agent therapy for preventing postoperative shivering with less side-
25 effects in patients undergo CABG.
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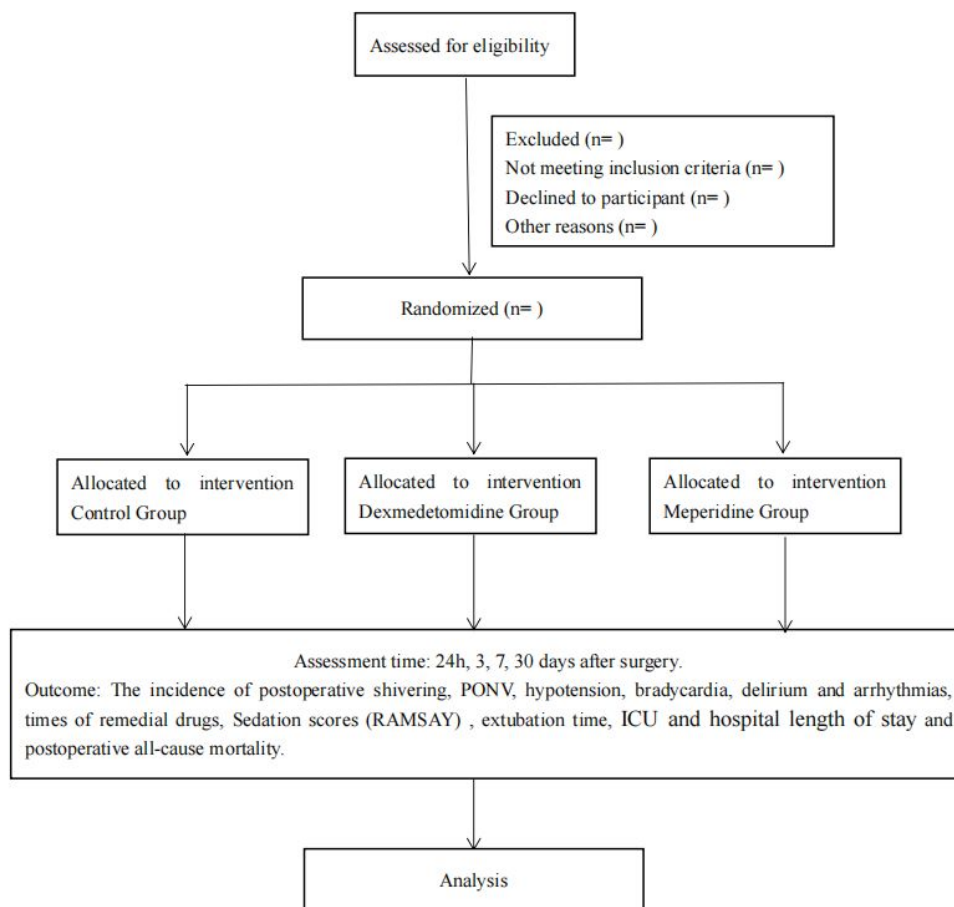
29 The aim of this study is to explore the efficacy and safety of dexmedetomidine for
30 preventing shivering after CABG and to compare the effects of dexmedetomidine and
31 meperidine on the incidence of shivering in patients undergo CABG.
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37 **METHODS AND ANALYSIS**

38 **Study design:**

39 This study is a prospective, single-centre, non-inferiority, double blinded, randomised
40 and placebo-controlled trial with three parallel arms (figure 1). It is designed to allocate
41 patients in an intended 1:1:1 allocation ratio to test the efficacy and safety of
42 dexmedetomidine for the prevention of postoperative shivering in patients undergo
43 elective CABG, and to compare the effectiveness of dexmedetomidine and meperidine
44 on the incidence of shivering in patients undergo CABG.
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47 This study is conducted according to the Standard Protocol Items: Recommendations
48 for Interventional Trials (SPIRIT), and SPIRIT 2013 Checklist has been included in
49 online additional file 1.
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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°C or less than 36°C, (5) postoperative hemodynamic instability, (6) preoperative use of left ventricular assistance device, (7) Patients with severe diabetic

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

9
10 A total of 180 patients will be randomly allocated to Dexmedetomidine group (group
11 Dex, n=60), Meperidine group (group M, n=60) and control group (group P, n=60).
12 Standard monitoring including ECG, non-invasive blood pressure (NIBP) and oxygen
13 saturation (SPO₂) will be used in all patients, radial artery catheterization and central
14 venous catheterization will also be conducted. The pulse rate, arterial blood pressure,
15 peripheral arterial oxygen saturation and nasopharyngeal temperature will be
16 continuously monitored and recorded at the time before study drug administration
17 (baseline) and 15,30, 60, 90 minutes after study drug administration. Neuromuscular
18 block monitor will be monitored by using a peripheral nerve stimulator intraoperatively.
19 The temperature of the operating room and ICU will be maintained at 22–25 °C.
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23 All patients will not receive premedication prior to induction of anesthesia.
24 Anesthesia will be induced with midazolam (0.05 mg/kg), propofol (1-2 mg/kg),
25 sufentanil (0.3 µg/kg) and atracurium (0.8 mg/kg) to facilitate tracheal intubation.
26 Propofol and remifentanyl will be continuously used during the surgery, and atracurium
27 (0.4 mg/kg) will be added if required.
28

29
30 In group Dex, 1 µg/kg dexmedetomidine will be continuously infused over 15
31 minutes. In group M, patients will receive meperidine 0.5 mg/kg intravenously. In
32 group P, patients will receive the same volume of normal saline according to the dose
33 of the two groups above.
34

35
36 Dexmedetomidine and meperidine will be given to the patients 30 minutes before the
37 end of surgery. If the shivering score developed to more than 2, 20 mg meperidine will
38 be injected intravenously. Patient-controlled intravenous analgesia (PCIA) will be used
39 for postoperative analgesia. Sufentanil, ondansetron, dezocine and saline were added
40 into PCA pump to a total of 100ml (the dose of all the analgesia agents are used
41 according to the patient's age and body weight). The PCIA is set at infusion rate of 2
42 ml/h, a bolus dose of 0.5 ml with a lock-out interval of 15 minutes. And the PCIA will
43 be used immediately after the operation to postoperative 48 hours. No reversal agents
44 will be administered. All patients will be transferred to ICU immediately after the
45 surgery.
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48 **Outcomes**

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50 Primary outcome:

51 The primary outcome of this study is the incidence of shivering within postoperative
52 24 hours.
53

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55 Secondary Outcomes:

- 56 1. Times of remedial drugs used after surgery within postoperative 24 hours.
- 57 2. The incidence of postoperative hypotension and bradycardia within postoperative
58 24 hours. Hypotension is defined as blood pressure less than 20% of baseline or systolic
59
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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 Scale¹⁸ 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.

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

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

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10 The participants will be randomly (computer-generated random number list) allocated
11 to either group Dex or group M or group P with a 1:1:1 allocation ratio. An investigator
12 not involved in participant registration and data collection will generate the allocation
13 sequence using a computer random number generator. This allocation sequence will
14 not be disclosed to ensure concealment until the completion of the trial.
15

16 According to the allocation sequence, a research assistant prepares the study drugs,
17 and the following experiments will be conducted by the investigator without knowing
18 the information of the study drugs.
19
20

21 **Blinding**

22
23 Both the patients and the investigators who participate in the intervention, observation
24 and assessment of this research will be unaware of the study drugs assignment and
25 group allocation until results have been analysed. All the study drugs will be
26 administrated in identical appearances and labels. During the study, group allocation
27 can be unmasked in order to protect the patient's safety. We can implement an urgent
28 unmasking if considered necessary for the sake of the patient's condition, and this will
29 not reveal the group allocations in other enrolled patients.
30
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33 **Data collection and management**

34 During the study, all the participants' information will be gained by the study form
35 which will be fulfilled by the investigator before the surgery. Outcomes include primary
36 and secondary outcomes will be followed up by at least one investigator of the study
37 team.
38
39

40 All the data will be recorded in the case report form (CRF) and synchronously input
41 into the electronic CRF. Personal information of participants will be kept confidentially,
42 and all data will be identified by a name acronym and a study identification number in
43 the CRF. The Paper data will be preserved in a locked cabinet. All of the research data
44 will be securely entered and filed in a designed Microsoft database for a minimum of
45 10 years after completion of the study. Only investigators of this study will have access
46 to these data.
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50 **Statistical methods**

51 Continuous variables will be presented as mean and standard deviation (SD) or median
52 and inter-quartile range (IQR) as appropriate. The categorical data will be described as
53 frequency, constituent ratio or percentage. One-way ANOVA and repeated measures
54 ANOVA will be used to compare the changes of continuous variables among the three
55 groups before and after treatment; Chi-square test will be used to compare the
56 difference between groups. The severity of postanaesthetic shivering, pain scores and
57 sedation scores will be compared by using Wilcoxon Rank Sum test. Statistical analyses
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3 will be performed using SPSS V.17.0 (Chicago, Illinois, USA). $P < 0.05$ was considered
4 statistically significant.
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7 **Ethics and dissemination**

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

17 This single-centre, randomised, placebo-controlled, double-blinded trial is designed to
18 investigate the effectiveness and safety of dexmedetomidine for the prevention of
19 postoperative shivering in patients undergo elective CABG, and to compare the
20 effectiveness of dexmedetomidine and meperidine on the incidence of shivering in
21 patients undergo CABG. In the present study, all enrolled patients will be admitted to
22 the ICU for postoperative care. Postoperative shivering will be evaluated according to
23 4 points scale of Wrench.¹⁰
24
25

26 This study has several strengths. This study is a well-designed single-centre,
27 randomised, placebo-controlled and double-blinded trial with large sample size. To our
28 knowledge, this is the new study to evaluate the impact of dexmedetomidine on
29 shivering in patients undergo CABG. The incidence of shivering is usually high in the
30 early recovery period of patients following cardiac surgery, especially in off-pump
31 CABG.²⁰ Thus, the incidence and severity assessment of shivering is performed in the
32 afternoon on the first day after the surgery. In addition, both dexmedetomidine and
33 meperidine are effective in preventing postoperative shivering, and will not have
34 influence on patients' prognosis. However, there are also several limitations in our
35 study. For example, there might be some hemodynamic effects of dexmedetomidine,
36 such as bradycardia and hypotension.²¹
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41 Although there is an increasing number of randomised controlled studies regarding
42 the prevention and treatment of postoperative shivering, the evidence of the effect on
43 dexmedetomidine in patients undergo elective CABG surgery is still sparse. The
44 potential significance of this study is that it may improve the effect of preventing
45 postoperative shivering in patients undergo elective CABG surgery, which can enhance
46 the recovery of patients after surgery and reduce the hospitalization time of patients.
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51 support in this study. The authors also thank all the participating patients.
52
53

54 **Author Contributions** ML planned the study. ML and C-pG designed the statistical
55 method. The work of patient recruitment and data collecting will be done by C-cC and
56 JY. The study drugs were prepared by C-sW. C-cC and ML drafted the protocol. Y-IW
57 and C-pG is the principal investigator of this study. All authors have read the
58 manuscript and approved the final protocol.
59
60

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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.

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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.

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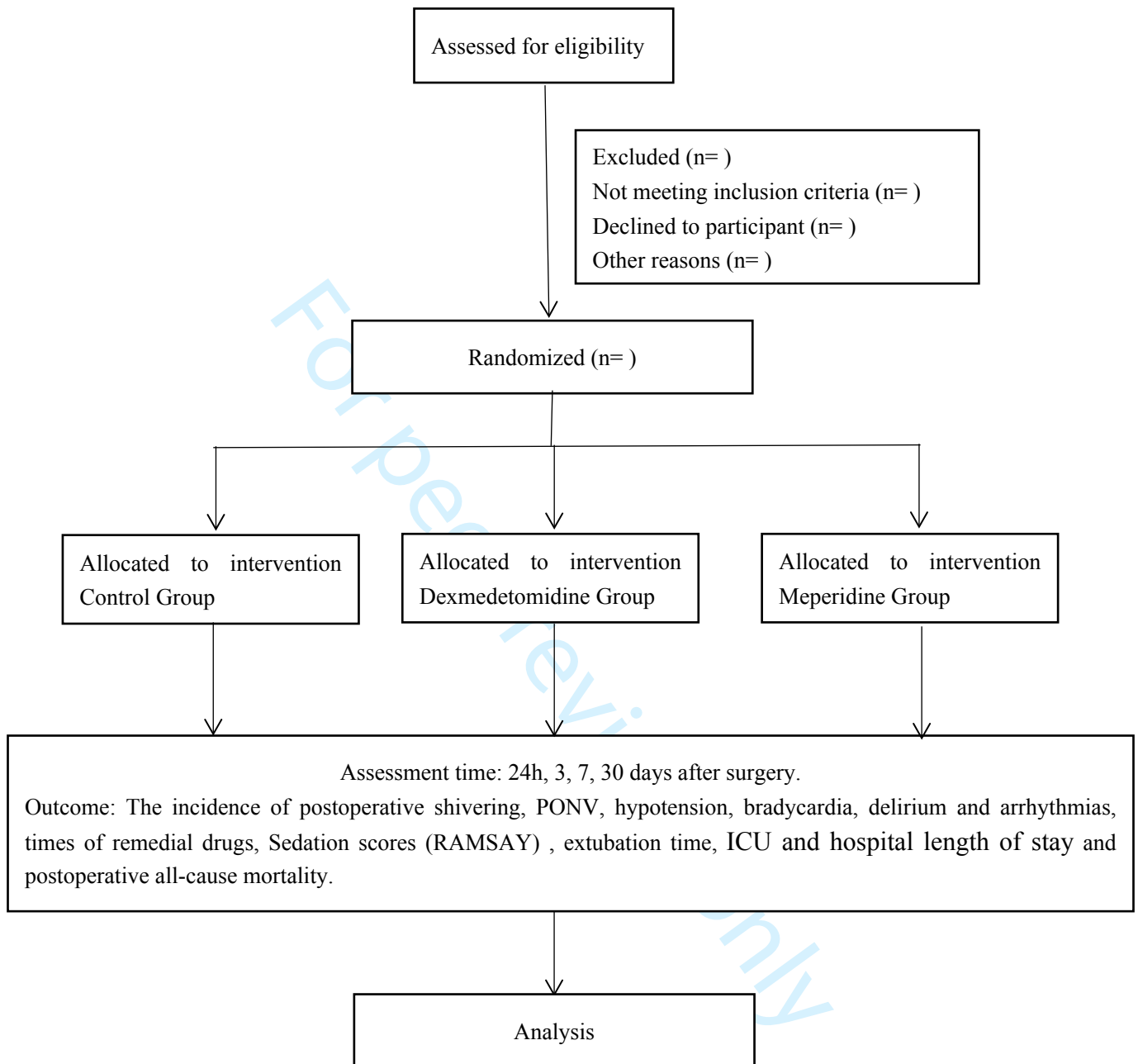


Figure 1 Consolidated Standards of Reporting Trials flow diagram. PONV, postoperative nausea and vomiting; ICU, intensive care unit.

	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								×	

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3 **Figure 2** Standard Protocol Items: Recommendations for Interventional Trials.

4 -t₁, the day before surgery; 0, day of surgery; t₁, 30 minutes before the end of surgery;
5 t₂, 15 minutes after study drugs administration; t₃, within postoperative 24 hours; t₄,
6 within postoperative 3 days; t₅, within postoperative 7 days; t₆, within postoperative 30
7 days.
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For peer review only

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 SPIRIT reporting guidelines, and cite them as:

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		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

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	9-10
9	responsibilities:		collection, management, analysis, and interpretation of	
10	sponsor and funder		data; writing of the report; and the decision to submit the	
11			report for publication, including whether they will have	
12			ultimate authority over any of these activities	
13				
14				
15				
16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
17	responsibilities:		centre, steering committee, endpoint adjudication	
18	committees		committee, data management team, and other individuals	
19			or groups overseeing the trial, if applicable (see Item 21a	
20			for data monitoring committee)	
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23				
24	Introduction			
25				
26				
27	Background and	#6a	Description of research question and justification for	2-3
28	rationale		undertaking the trial, including summary of relevant	
29			studies (published and unpublished) examining benefits	
30			and harms for each intervention	
31				
32				
33				
34	Background and	#6b	Explanation for choice of comparators	2-3
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	#7	Specific objectives or hypotheses	3
40				
41	Trial design	#8	Description of trial design including type of trial (eg,	3-4
42			parallel group, crossover, factorial, single group),	
43			allocation ratio, and framework (eg, superiority,	
44			equivalence, non-inferiority, exploratory)	
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46				
47				
48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
52				
53				
54				
55	Study setting	#9	Description of study settings (eg, community clinic,	4
56			academic hospital) and list of countries where data will be	
57			collected. Reference to where list of study sites can be	
58				
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1		obtained	
2	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
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9	Interventions: description	#11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
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14	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
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21	Interventions: adherence	#11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
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27	Interventions: concomitant care	#11d Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
28			
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30	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
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42	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
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49	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
50			
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55	Recruitment	#15 Strategies for achieving adequate participant enrolment to reach target sample size	7-8
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1 **Methods:**

2 **Assignment of** 3 **interventions (for** 4 **controlled trials)**

5 6 7 8 9 10 11 12 13 14 15 16 17 18	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
19 20 21 22 23 24 25	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
26 27 28 29 30	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
31 32 33 34 35	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
36 37 38 39 40	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

41 **Methods: Data** 42 **collection,** 43 **management, and** 44 **analysis**

45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	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
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1		protocol	
2	Data collection plan:	#18b	Plans to promote participant retention and complete
3	retention		follow-up, including list of any outcome data to be
4			collected for participants who discontinue or deviate from
5			intervention protocols
6			
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9	Data management	#19	Plans for data entry, coding, security, and storage,
10			including any related processes to promote data quality
11			(eg, double data entry; range checks for data values).
12			Reference to where details of data management
13			procedures can be found, if not in the protocol
14			
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16			
17	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary
18			outcomes. Reference to where other details of the
19			statistical analysis plan can be found, if not in the protocol
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21			
22			
23	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and
24	analyses		adjusted analyses)
25			
26			
27	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-
28	population and		adherence (eg, as randomised analysis), and any
29	missing data		statistical methods to handle missing data (eg, multiple
30			imputation)
31			
32			
33	Methods: Monitoring		
34			
35			
36	Data monitoring:	#21a	Composition of data monitoring committee (DMC);
37	formal committee		summary of its role and reporting structure; statement of
38			whether it is independent from the sponsor and competing
39			interests; and reference to where further details about its
40			charter can be found, if not in the protocol. Alternatively,
41			an explanation of why a DMC is not needed
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46	Data monitoring:	#21b	Description of any interim analyses and stopping
47	interim analysis		guidelines, including who will have access to these interim
48			results and make the final decision to terminate the trial
49			
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51	Harms	#22	Plans for collecting, assessing, reporting, and managing
52			solicited and spontaneously reported adverse events and
53			other unintended effects of trial interventions or trial
54			conduct
55			
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58	Auditing	#23	Frequency and procedures for auditing trial conduct, if
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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	-

1	authorship	professional writers	
2	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,
3	reproducible research		participant-level dataset, and statistical code
4			-

6 Appendices

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

19 None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative
 20 Commons Attribution License CC-BY-NC. This checklist can be completed online using
 21 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with
 22 [Penelope.ai](#)
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BMJ Open

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

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Manuscript ID	bmjopen-2021-053865.R1
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Manuscripts

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

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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,

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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

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2
3 postanesthetic shivering.⁶⁻¹² However, there are few studies on the pharmacological
4 interventions used for preventing shivering after CABG.

5
6 Dexmedetomidine is a highly selective α_2 -adrenoceptor agonist with an eight-fold
7 higher affinity for the α_2 -adrenoceptor than clonidine, which can cause sedation,
8 analgesia, anxiolysis, and attenuation of the neuroendocrine and hemodynamic
9 responses to anesthesia and surgery.^{13 14} It may also provide a deeper level of sedation,
10 decrease the incidence of postoperative nausea and vomiting (PONV), and increase
11 hemodynamic stability during a sudden increase in stress.¹⁵ Previous studies have
12 shown that dexmedetomidine can reduce the incidence of shivering after both spinal
13 and general anesthesia.¹⁵ Nevertheless, the effects of dexmedetomidine on the
14 incidence of shivering have not been reported in patients after CABG.

15
16 Meperidine is a combination of μ - and κ -receptor agonists. It can prevent
17 hypothermia with peripheral vasoconstriction and central vasodilatation. Numerous
18 trials have confirmed that meperidine is effectively used for the prevention and
19 treatment of perioperative shivering.^{16 17} Meperidine has some side effects such as
20 nausea, vomiting, and respiratory depression, especially in patients who have
21 previously used opioids or anesthetics and experienced hallucinations.¹⁸ Therefore, it is
22 important to find an effective agent therapy for preventing postoperative shivering with
23 fewer side effects in patients undergoing CABG.

24
25 The aim of this study is to compare the effects of dexmedetomidine and meperidine
26 on the incidence of shivering in patients undergoing CABG.

27 28 29 30 31 32 **METHODS AND ANALYSIS**

33 **Study design:**

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

39
40 This study protocol is written according to the Standard Protocol Items:
41 Recommendations for Interventional Trials (SPIRIT); the SPIRIT 2013 checklist has
42 been included in Online Additional File 1.

43 44 45 46 **Study setting**

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

49 50 51 **Participants**

52 **Inclusion criteria**

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

57 58 59 **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) 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 (SPO₂) 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 µg/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 Scale¹⁹ 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

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3 studies, we assumed that the incidence of shivering in group Dex and group M was 23%
4 and 46.48%, respectively.^{20 21} Based on these parameters, we calculated the sample size
5 of 55 patients per group. To compensate for potential dropouts or inadequate procedures,
6 we assumed an attrition rate of 5% and determined that 60 patients will be required in
7 each group, to make a total of 180 patients.
8
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10 11 **Recruitment**

12 Participants who meet the inclusion criteria are currently recruited for the study. The
13 purpose, procedures, and potential risks and benefits of this study will be described to
14 each patient and written informed consent will be obtained. If the patient cannot provide
15 consent, written informed consent will be obtained from their authorized
16 representatives. The patient will be assured that they are free to decline consent without
17 consequences, and they can withdraw consent at any time without affecting treatment.
18
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21 22 **Allocation and randomization**

23 The participants will be randomly allocated to either group Dex, group M, or group P
24 with a 1:1:1 allocation ratio. The random sequence will be conducted via a computer-
25 generated random number list by an investigator not involved in participant registration
26 and data collection. This allocation sequence will be packed within sealed opaque
27 envelopes and will not be disclosed to ensure concealment until the completion of the
28 trial.
29

30 According to the allocation sequence, a research assistant will prepare the study
31 drugs and the following experiments will be conducted by a blinded investigator.
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34 35 **Blinding**

36 Both the patients and the investigators who participate in the intervention, observation,
37 and assessment of this research will be unaware of the study drug assignment and group
38 allocation until the results are analyzed. All the study drugs will be administered with
39 identical appearances and labels. During the study, group allocation could be unmasked
40 to protect the patient's safety. We can implement urgent unmasking if considered
41 necessary for the sake of the patient's condition, and this will not reveal the group
42 allocations of the other enrolled patients.
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46 47 **Data collection and management**

48 During the study, all participant information will be gained by the study form, which
49 will be filled out by an investigator before the surgery. Outcomes, including primary
50 and secondary outcomes, will be followed up by at least one investigator from the study
51 team.
52

53 All the data will be recorded in the case report form (CRF) and synchronously input
54 into the electronic CRF. Personal information of participants will be kept confidential,
55 and all data will be identified by a name acronym and a study identification number in
56 the CRF. The paper data will be preserved in a locked cabinet. All research data will be
57 securely entered and filed in a designed Microsoft database for a minimum of 10 years
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3 after completion of the study. Only the investigators in this study will have access to
4 these data.
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6 7 **Statistical methods**

8 Continuous variables will be presented as mean and standard deviation (SD) or median
9 and interquartile range (IQR), as appropriate. Categorical data will be described as
10 frequencies, constituent ratios, or percentages. One-way ANOVA and repeated
11 measures ANOVA will be used to compare the changes in continuous variables among
12 the three groups before and after treatment, and the chi-squared test will be used to
13 compare the differences between groups. The severity of postanesthetic shivering, pain
14 scores, and sedation scores will be compared using the Wilcoxon rank sum test.
15 Statistical analyses will be performed using SPSS 22.0, and statistical significance is
16 set at $P < 0.05$.
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20 21 **Ethics and dissemination**

22 The study protocol was approved by the ethics committee of The First Affiliated
23 Hospital of Shandong First Medical University (YXLL-KY-2021(002)) and registered
24 at ClinicalTrials.gov. The results of this trial will be presented at national and
25 international scientific meetings or conferences and published in peer-reviewed
26 international scientific journals.
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29

30 31 **Patient and public involvement**

32 There were no patients nor members of the public involved in recruitment or
33 development of the study design and outcome measures.
34
35

36 **DISCUSSION**

37 This single-center, randomized, placebo-controlled, double-blinded trial was designed
38 to compare the effectiveness of dexmedetomidine and meperidine on the incidence of
39 shivering in patients undergoing off-pump CABG. Postoperative shivering will be
40 evaluated according to the 4-point Wrench scale.²²
41

42 This study has several strengths. It is a well-designed, single-center, randomized,
43 placebo-controlled, double-blinded trial with a large sample size. To our knowledge,
44 this is the first study to evaluate the impact of dexmedetomidine on shivering in patients
45 undergoing CABG. The incidence of shivering is usually high in the early recovery
46 period of patients following cardiac surgery, especially in off-pump CABG.²³ Thus, the
47 incidence and severity assessment of shivering is performed in the afternoon on the first
48 day after the surgery. In addition, both dexmedetomidine and meperidine are effective
49 in preventing postoperative shivering and do not influence patient prognosis. However,
50 our study has several limitations. For example, there might be some hemodynamic
51 effects of dexmedetomidine, such as bradycardia and hypotension.²⁴
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53
54
55

56 **Acknowledgements** The authors thank all the contributors and collaborators for their
57 support in this study. The authors also thank all the participating patients.
58
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1
2
3 **Author Contributions** ML planned the study. ML and C-pG designed the statistical
4 method. The work of patient recruitment and data collecting will be done by C-cC and
5 JY. The study drugs were prepared by C-sW. C-cC and ML drafted the protocol. C-pG
6 is the principal investigator of this study. All authors have read the manuscript and
7 approved the final protocol.
8
9

10
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18
19 **Competing interests** None declared.
20

21 **Patient consent for publication** Not required.
22

23
24 **Provenance and peer review** Not commissioned; externally peer reviewed.
25

26
27 **Data availability statement** Not applicable.
28

29
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40 **Abbreviation** CABG, coronary artery bypass graft; ASA, American Society of
41 Anaesthesiologists'; ICU, intensive care unit; PONV, postoperative nausea and
42 vomiting; ECG, electrocardiography; NIBP, non-invasive blood pressure; SPO₂,
43 oxygen saturation; PCIA, Patient-controlled intravenous analgesia; CRF, case report
44 form.
45
46

47 **Figure caption:**

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

50 **Figure 2** Standard Protocol Items: Recommendations for Interventional Trials.

51
52 -t1, the day before surgery; 0, day of surgery; t1, 30 minutes before the end of surgery;
53 t2, 15 minutes after study drug administration; t3, within postoperative 24 hours; t4,
54 within postoperative 3 days; t5, within postoperative 7 days; t6, within postoperative
55 30 days.
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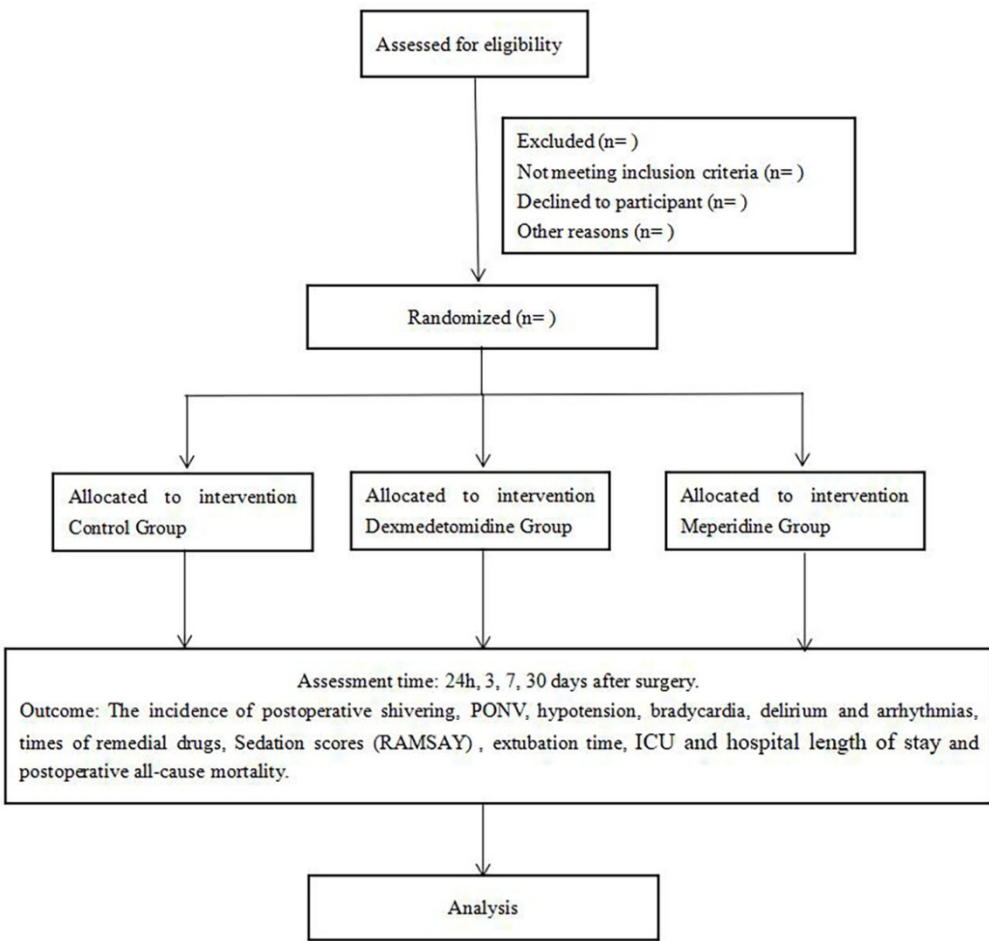
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TIMEPOINT	STUDY PERIOD									
	Enrolment	Allocation	Post-allocation						Close-out	
	-t1	0	t1	t2	t3	t4	t5	t6	After end of participation	
ENROLLMENT:										
Eligibility screen	×									
Informed consent	×									
Allocation		×								
INTERVENTIONS:										
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.

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		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

1	Roles and	#5b	Name and contact information for the trial sponsor	n/a
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	n/a
8	responsibilities:		collection, management, analysis, and interpretation of	
9	sponsor and funder		data; writing of the report; and the decision to submit the	
10			report for publication, including whether they will have	
11			ultimate authority over any of these activities	
12				
13				
14				
15	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
16	responsibilities:		centre, steering committee, endpoint adjudication	
17	committees		committee, data management team, and other individuals	
18			or groups overseeing the trial, if applicable (see Item 21a	
19			for data monitoring committee)	
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21				
22				
23				
24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for	2-3
27	rationale		undertaking the trial, including summary of relevant	
28			studies (published and unpublished) examining benefits	
29			and harms for each intervention	
30				
31				
32				
33	Background and	#6b	Explanation for choice of comparators	3
34	rationale: choice of			
35	comparators			
36				
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38	Objectives	#7	Specific objectives or hypotheses	3
39				
40				
41	Trial design	#8	Description of trial design including type of trial (eg,	3
42			parallel group, crossover, factorial, single group),	
43			allocation ratio, and framework (eg, superiority,	
44			equivalence, non-inferiority, exploratory)	
45				
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47				
48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
52				
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54	Study setting	#9	Description of study settings (eg, community clinic,	3
55			academic hospital) and list of countries where data will be	
56			collected. Reference to where list of study sites can be	
57				
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		obtained	
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2	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			3-4
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9	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
10			4-5
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14	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)
15			n/a
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21	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)
22			n/a
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27	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
28			4-5
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31	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
32			5
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42	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)
43			5
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49	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
50			6
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55	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size
56			6
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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
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1		protocol	
2	Data collection plan:	#18b	Plans to promote participant retention and complete
3	retention		follow-up, including list of any outcome data to be
4			collected for participants who discontinue or deviate from
5			intervention protocols
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9	Data management	#19	Plans for data entry, coding, security, and storage,
10			including any related processes to promote data quality
11			(eg, double data entry; range checks for data values).
12			Reference to where details of data management
13			procedures can be found, if not in the protocol
14			
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16			
17	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary
18			outcomes. Reference to where other details of the
19			statistical analysis plan can be found, if not in the protocol
20			
21			
22			
23	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and
24	analyses		adjusted analyses)
25			
26			
27	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-
28	population and		adherence (eg, as randomised analysis), and any
29	missing data		statistical methods to handle missing data (eg, multiple
30			imputation)
31			
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33	Methods: Monitoring		
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36	Data monitoring:	#21a	Composition of data monitoring committee (DMC);
37	formal committee		summary of its role and reporting structure; statement of
38			whether it is independent from the sponsor and competing
39			interests; and reference to where further details about its
40			charter can be found, if not in the protocol. Alternatively,
41			an explanation of why a DMC is not needed
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46	Data monitoring:	#21b	Description of any interim analyses and stopping
47	interim analysis		guidelines, including who will have access to these interim
48			results and make the final decision to terminate the trial
49			
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51	Harms	#22	Plans for collecting, assessing, reporting, and managing
52			solicited and spontaneously reported adverse events and
53			other unintended effects of trial interventions or trial
54			conduct
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58	Auditing	#23	Frequency and procedures for auditing trial conduct, if
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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	-

1	authorship	professional writers	
2	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, -
3	reproducible research		participant-level dataset, and statistical code
4			
5			

6 Appendices

7			
8	Informed consent	#32	Model consent form and other related documentation n/a
9	materials		given to participants and authorised surrogates
10			
11			
12	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of n/a
13			biological specimens for genetic or molecular analysis in
14			the current trial and for future use in ancillary studies, if
15			applicable
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19 None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative
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 22 [Penelope.ai](#)
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BMJ Open

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

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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

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

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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

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3 surgery, the incidence of postoperative hypotension and bradycardia, sedation scores,
4 endotracheal extubation time, intensive care unit (ICU) length of stay, incidence of
5 postoperative delirium within 7 days after surgery, incidence of postoperative
6 arrhythmias, incidence of postoperative nausea and vomiting (PONV), average
7 hospital length of stay, and mortality rate 30 days after surgery.
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10 **Ethics and dissemination:** The study protocol was approved by the ethics committee
11 of The First Affiliated Hospital of Shandong First Medical University on January 20,
12 2021 (YXLL-KY-2021(002)) and registered at ClinicalTrials.gov. The results of this
13 study will be presented at national and international scientific meetings and conferences.
14 We plan to publish the data in peer-reviewed international scientific journals.
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17 **ARTICLE SUMMARY**

18 **Strengths and limitations of this study**

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

34 Shivering is a common complication in patients during the postoperative period, with
35 a reported incidence ranging from 5% to 65% in general anesthesia and 33% in epidural
36 anesthesia.¹ The most common causes of shivering are hypothermia, blood transfusion,
37 and pain. Patients with hypothermia after coronary artery bypass graft (CABG)
38 surgery (< 36 °C) usually have a higher mortality rate and prolonged length of hospital
39 stay.²
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42 Shivering can increase the perioperative risk, and especially the risk of myocardial
43 ischemia, in patients with coronary artery disease due to increased oxygen consumption
44 (by 100%–600%). Moreover, interference with electrocardiography (ECG) and blood
45 pressure monitoring, increased intracranial and intraocular pressure, increased
46 production of carbon dioxide, and circulating catecholamines are also known side
47 effects.^{3 4} Therefore, it is important to prevent shivering after CABG. The incidence of
48 postoperative shivering is still high, although some non-pharmacological methods, such
49 as heating blankets or warming the administered fluid, have been used postoperatively.⁵
50 Some medical agents, such as nefopam, tramadol, meperidine, morphine, fentanyl,
51 doxapram, ketamine, and nalbuphine, have been reported to be effective in preventing
52 postanesthetic shivering.⁶⁻¹² However, there are few studies on the pharmacological
53 interventions used for preventing shivering after CABG.
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58 Dexmedetomidine is a highly selective α_2 -adrenoceptor agonist with an eight-fold
59 higher affinity for the α_2 -adrenoceptor than clonidine, which can cause sedation,
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3 analgesia, anxiolysis, and attenuation of the neuroendocrine and hemodynamic
4 responses to anesthesia and surgery.^{13 14} It may also provide a deeper level of sedation,
5 decrease the incidence of postoperative nausea and vomiting (PONV), and increase
6 hemodynamic stability during a sudden increase in stress.¹⁵ Previous studies have
7 shown that dexmedetomidine can reduce the incidence of shivering after both spinal
8 and general anesthesia.¹⁵ Nevertheless, the effects of dexmedetomidine on the
9 incidence of shivering have not been reported in patients after CABG.

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

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

26 METHODS AND ANALYSIS

28 Study design:

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

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

41 Study setting

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

46 Participants

47 Inclusion criteria

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

54 Exclusion criteria

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

preoperative use of a left ventricular assistance device, (7) 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 (SPO₂) 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 remifentanyl 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 µg/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 Scale¹⁹ 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

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3 each group, to make a total of 180 patients.
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6 **Recruitment**

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

17 The participants will be randomly allocated to either group Dex, group M, or group P
18 with a 1:1:1 allocation ratio. The random sequence will be conducted via a computer-
19 generated random number list by an investigator not involved in participant registration
20 and data collection. This allocation sequence will be packed within sealed opaque
21 envelopes and will not be disclosed to ensure concealment until the completion of the
22 trial.
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25 According to the allocation sequence, a research assistant will prepare the study
26 drugs and the following experiments will be conducted by a blinded investigator.
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29 **Blinding**

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

42 During the study, all participant information will be gained by the study form, which
43 will be filled out by an investigator before the surgery. Outcomes, including primary
44 and secondary outcomes, will be followed up by at least one investigator from the study
45 team.
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47 All the data will be recorded in the case report form (CRF) and synchronously input
48 into the electronic CRF. Personal information of participants will be kept confidential,
49 and all data will be identified by a name acronym and a study identification number in
50 the CRF. The paper data will be preserved in a locked cabinet. All research data will be
51 securely entered and filed in a designed Microsoft database for a minimum of 10 years
52 after completion of the study. Only the investigators in this study will have access to
53 these data.
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58 **Statistical methods**

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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

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Author Contributions ML and Y-IW 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.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Not applicable.

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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.

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.

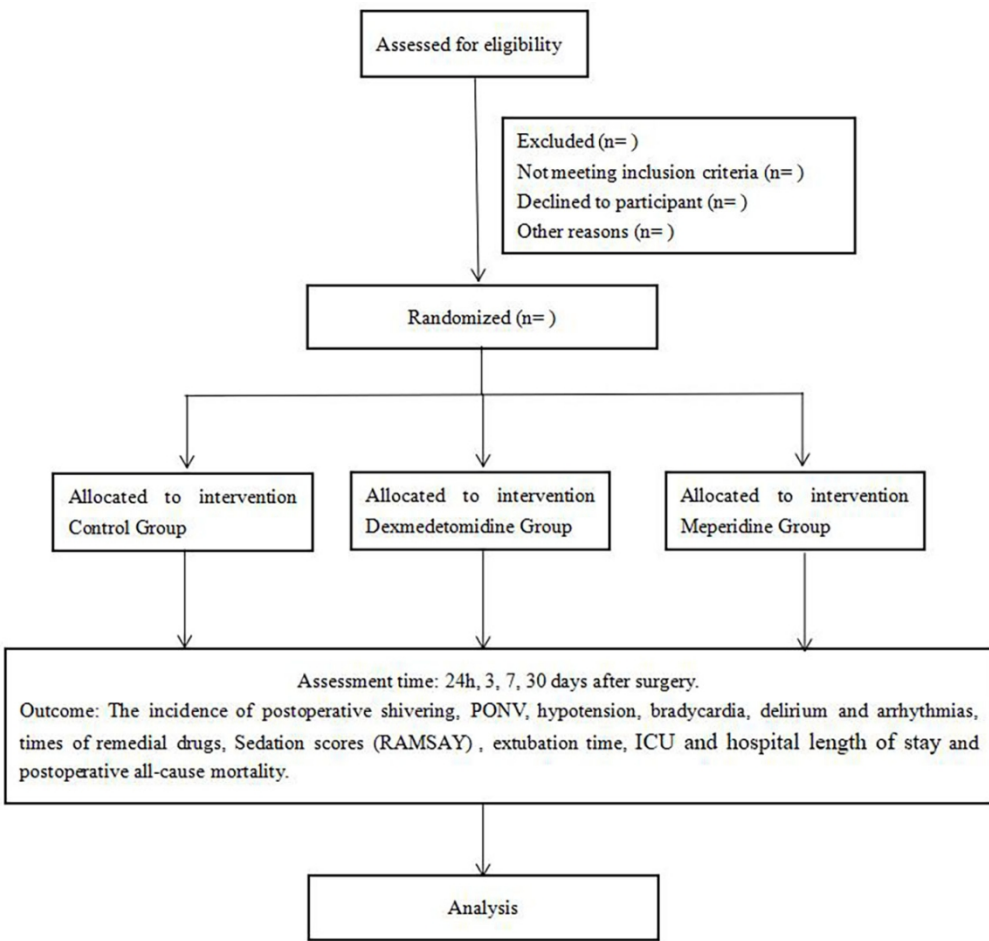
-t1, the day before surgery; 0, day of surgery; t1, 30 minutes before the end of surgery; t2, 15 minutes after study drug administration; t3, within postoperative 24 hours; t4, within postoperative 3 days; t5, within postoperative 7 days; t6, within postoperative 30 days.

word count 2633

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TIMEPOINT	STUDY PERIOD									
	Enrolment	Allocation	Post-allocation						Close-out	
	-t1	0	t1	t2	t3	t4	t5	t6	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 SPIRIT reporting 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

1	Roles and	#5b	Name and contact information for the trial sponsor	n/a
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	n/a
8	responsibilities:		collection, management, analysis, and interpretation of	
9	sponsor and funder		data; writing of the report; and the decision to submit the	
10			report for publication, including whether they will have	
11			ultimate authority over any of these activities	
12				
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14				
15	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
16	responsibilities:		centre, steering committee, endpoint adjudication	
17	committees		committee, data management team, and other individuals	
18			or groups overseeing the trial, if applicable (see Item 21a	
19			for data monitoring committee)	
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24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for	2-3
27	rationale		undertaking the trial, including summary of relevant	
28			studies (published and unpublished) examining benefits	
29			and harms for each intervention	
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33	Background and	#6b	Explanation for choice of comparators	3
34	rationale: choice of			
35	comparators			
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38	Objectives	#7	Specific objectives or hypotheses	3
39				
40				
41	Trial design	#8	Description of trial design including type of trial (eg,	3
42			parallel group, crossover, factorial, single group),	
43			allocation ratio, and framework (eg, superiority,	
44			equivalence, non-inferiority, exploratory)	
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48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
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54	Study setting	#9	Description of study settings (eg, community clinic,	3
55			academic hospital) and list of countries where data will be	
56			collected. Reference to where list of study sites can be	
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		obtained	
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2	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
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9	Interventions: description	#11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-5
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14	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
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21	Interventions: adherence	#11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
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27	Interventions: concomitant care	#11d Relevant concomitant care and interventions that are permitted or prohibited during the trial	4-5
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30	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
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41	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
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48	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
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55	Recruitment	#15 Strategies for achieving adequate participant enrolment to reach target sample size	6
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1 **Methods:**

2 **Assignment of** 3 **interventions (for** 4 **controlled trials)**

5 6 7 8 9 10 11 12 13 14 15 16 17 18	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
19 20 21 22 23 24 25	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
26 27 28 29 30	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
31 32 33 34 35	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
36 37 38 39 40	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

41 **Methods: Data** 42 **collection,** 43 **management, and** 44 **analysis**

45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	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
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1		protocol	
2	Data collection plan:	#18b	Plans to promote participant retention and complete
3	retention		follow-up, including list of any outcome data to be
4			collected for participants who discontinue or deviate from
5			intervention protocols
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9	Data management	#19	Plans for data entry, coding, security, and storage,
10			including any related processes to promote data quality
11			(eg, double data entry; range checks for data values).
12			Reference to where details of data management
13			procedures can be found, if not in the protocol
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17	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary
18			outcomes. Reference to where other details of the
19			statistical analysis plan can be found, if not in the protocol
20			
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23	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and
24	analyses		adjusted analyses)
25			
26			
27	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-
28	population and		adherence (eg, as randomised analysis), and any
29	missing data		statistical methods to handle missing data (eg, multiple
30			imputation)
31			
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33	Methods: Monitoring		
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36	Data monitoring:	#21a	Composition of data monitoring committee (DMC);
37	formal committee		summary of its role and reporting structure; statement of
38			whether it is independent from the sponsor and competing
39			interests; and reference to where further details about its
40			charter can be found, if not in the protocol. Alternatively,
41			an explanation of why a DMC is not needed
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46	Data monitoring:	#21b	Description of any interim analyses and stopping
47	interim analysis		guidelines, including who will have access to these interim
48			results and make the final decision to terminate the trial
49			
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51	Harms	#22	Plans for collecting, assessing, reporting, and managing
52			solicited and spontaneously reported adverse events and
53			other unintended effects of trial interventions or trial
54			conduct
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58	Auditing	#23	Frequency and procedures for auditing trial conduct, if
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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	-

1	authorship	professional writers	
2	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, -
3	reproducible research		participant-level dataset, and statistical code
4			
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6 Appendices

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8	Informed consent	#32	Model consent form and other related documentation n/a
9	materials		given to participants and authorised surrogates
10			
11	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of n/a
12			biological specimens for genetic or molecular analysis in
13			the current trial and for future use in ancillary studies, if
14			applicable
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