

# Nocturnal dexmedetomidine for prevention of delirium in critically ill surgical patients: a randomized control trial protocol

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## ABSTRACT:

**Background:** Nocturnal or postoperative dexmedetomidine has been shown to reduce the incidence of delirium in critically ill surgical patients without an increase in any complications. However, it is not clear whether dexmedetomidine has preventive effects against delirium in the patients with high risk of postoperative delirium (POD) since no previous studies have clearly emphasized on high-risk surgical patients.

**Methods:** In this single-center, double-blind, randomized controlled trial, we randomize 114 high risk POD patients defined by developed predictive scores and admitted to surgical intensive care units (SICUs) into 2 groups: nocturnal dexmedetomidine (9 pm – 6 am) and placebo. The outcomes were incidence of POD, delirium-free days, secondary delirium-related complications and concerned complications including hypotension and bradycardia. Other treatments apart from intervention are standardized. Intention to treat analysis is used to analyze all data.

**Hypothesis:** We hypothesize that nocturnal dexmedetomidine giving to high-risk POD patients admitted to SICUs postoperatively would (1) reduce incidence of POD (2) improve delirium-free days (3) reduce secondary delirium-related complications (4) show no difference in hypotension and bradycardia between groups.

**Ethics and dissemination:** The trial receives ethic approval from Siriraj Institutional Review Board. We plan to disseminate the results in peer-reviewed critical care medicine or anesthesiology-related journals, conferences nationally and internationally.

**Trial registration:** TCTR20210217001

**Keywords:** Dexmedetomidine, Surgical intensive care, Postoperative delirium, Prevention

## INTRODUCTION

Delirium is defined as acute and fluctuating disturbance of consciousness with reduced ability to focus, maintain, or shift attention, accompanied by change in cognition and perceptual disturbances secondary to a general medical condition. Postoperative delirium (POD) is a form of delirium occurring in patients who have undergone surgery and anesthesia, usually between one and three days after an operation.[1] Delirium is not uncommon in critically ill adults. However, delirium encountered in intensive care units (ICU) and other settings are assumed to be equivalent pathophysiologic states. Delirium is a clinical diagnosis. The majority of studies in ICUs detect delirium using screening tools such as Confusion Assessment Method for ICU (CAM-ICU)[2] or intensive care delirium screening checklist (ICDSC).[3] POD occurs in 17–61% of major surgical procedures.[4] The incidence increases with a high burden of comorbidities presenting as multiorgan dysfunction before surgery. It may be associated with cognitive decline, prolonged LOS, decreased functional independence, increased risk of dementia, caregiver burden, health care costs, morbidity and mortality. [4–6] Therefore, prevention of POD should be the aim in patients having potential predisposing factors to develop delirium after surgery including higher age, history of dementia and multiple comorbidities.[2, 6, 7]

Regarding identification of high-risk patients in ICUs, the previous study in our institution by Chaiwat, et al. on incidence, risk factors, and predictive scores of POD in critically ill surgical patients in Siriraj Hospital found that the incidence was 24.1%.[8] This study focuses on identification of high-risk patients by development of following predictive score: age + (5 × SOFA (Sequential Organ Failure Assessment) score) + (15 × Benzodiazepine use) + (20 × having diabetes mellitus) + (20 × on mechanical ventilation) + (20 × having modified IQCODE (Modified Informant Questionnaire on Cognitive Decline in the Elderly) > 3.42). The cut point score of 125 demonstrates the best sensitivity (72 %), specificity (81%) and area under curve (AUC) (0.84).[8] After external and internal validation, the optimal cut off point was found to be > 115, which demonstrates the highest sensitivity (79%) and specificity (71%).

While many non-pharmacologic interventions have been proven to be beneficial including reorientation, nonpharmacologic sleep protocol, getting patient out of bed and walking, encouraging use of eyeglasses and hearing aids, encouraging fluid intake, proactive geriatric consultation, reducing opioid use, and discontinuing standing orders for sleeping pills, the effectiveness of pharmacologic approaches for delirium prevention in ICU setting remains unclear.[2, 6, 7]

Dexmedetomidine is a selective  $\alpha_2$  agonist with effects of anxiolysis, sedation, and modest analgesia with minimal respiratory depression. It has become a popular sedative agent in ICU because of its ability to produce cooperative sedation, maintain respiratory drive and not produce any agitation. In addition, it helps to maintain natural sleep during sedation resulting in speedy recovery time in ICU.[9]

Su, et al. studied the effect of low dose intravenous dexmedetomidine in prevention of POD in older adult patients after non-cardiac surgery. The study showed incidence of POD was significantly lower in patients receiving intravenous dexmedetomidine (0.1  $\mu\text{g}/\text{kg}/\text{h}$  from ICU admission

## KEY MESSAGES:

- This study compares the preventive effect against postoperative delirium (POD) of nocturnal dexmedetomidine (9 pm – 6 am) to placebo in high-risk surgical patients. We hypothesize that nocturnal dexmedetomidine would reduce incidence of POD and improve delirium-free days without difference in hypotension and bradycardia between two groups.

on day of surgery until 8 am on postoperative day 1) than in the placebo group, while the occurrence of hypotension and bradycardia did not differ between two groups.[10] Nevertheless, this study did not use any predictive score to identify the high risk surgical patients so some predisposing factors such as history of dementia and baseline delirium assessment were not assessed.

Another study by Skrobik, et al. found nocturnal (9:30 pm to 6:15 am) intravenous dexmedetomidine (0.2  $\mu\text{g}/\text{kg}/\text{h}$ , maximum dose up to 0.7  $\mu\text{g}/\text{kg}/\text{h}$ ) was associated with greater proportion of patients remaining delirium-free during ICU stay compared to placebo. [11] Even though the study reported Prediction of Delirium in ICU Patients (PRE-DELIRIC) risk score but it was not used at initial screening process. Moreover, this study included both medical and surgical patients.

It is not clear whether dexmedetomidine has preventive effect against delirium in patients with high risk of POD, since no earlier studies have clearly emphasized high-risk surgical patients. In addition, we have created predictive score in our population and validated this score in other institutions with the same population (The study has been submitted). Given that dexmedetomidine's availability is considerably more limited than other sedative agents in our setting, routine use for sedation in general patients might not be reasonable. Therefore, the aim of the current study is to evaluate the effect of nocturnal dexmedetomidine in prevention of POD in critically ill surgical patients with high risk of POD.

## OBJECTIVES

### Primary Objective

Primary objective is to identify whether nocturnal dexmedetomidine in high-risk patients admitted to SICUs after non-cardiac surgery would prevent postoperative delirium.

### Secondary Objectives

Secondary objective is to identify incidence of adverse outcomes from nocturnal dexmedetomidine after non-cardiac surgery (hypotension, bradycardia) and to compare secondary delirium-related outcomes including episode of nosocomial infection, duration of mechanical ventilation, ICU length of stay (ICU-LOS), hospital length of stay (hospital-LOS) and in-hospital mortality between intervention and placebo groups.

## MATERIAL AND METHODS

### Study Design

Randomized, double-blind, placebo, controlled trial.

### Study Setting

Patients with high risk for postoperative delirium undergoing non-cardiac surgery and postoperatively admitted to surgical intensive care units (SICUs), Siriraj Hospital, Mahidol University.

### Eligibility Criteria

#### Inclusion criteria

1. Age 18 years or older undergoing non-cardiac surgery.
2. Admitted to SICU immediately after surgery (before 6 pm on the day of surgery).
3. A predictive score of postoperative delirium of 115 or more (age+(5×SOFA score) + (15×Benzodiazepine use) + (20×DM) + (20×mechanical ventilation) + (20×modified IQCODE > 3.42)).
4. Expected to stay in SICU for more than 24 hours.

#### Exclusion criteria

1. Unable to communicate in Thai
2. Preoperative history of schizophrenia, epilepsy, Parkinsonism, myasthenia gravis
3. Inability to communicate in the preoperative period (coma, profound dementia, or language barrier)
4. Admitted with a primary neurologic condition or injury
5. Known preoperative LVEF less than 30%
6. Sick sinus syndrome, severe sinus bradycardia (<50 beats per min [bpm]), or second-degree or greater atrioventricular block without pacemaker
7. Child-Pugh class C
8. Serious renal dysfunction (undergoing dialysis before surgery)
9. Known allergies or anaphylaxis of dexmedetomidine, propofol, midazolam, haloperidol
10. Expected death within 48 hours after surgery
11. Inability to obtain informed consent
12. Pregnancy

#### Withdrawal criteria

1. Participant(s) and/or proxies desire to quit the study
2. Clinical changes causing inability to evaluate RASS score.

#### Participant Selection and Recruitment

The research team screen potential participants during pre-anesthesia evaluation (elective case with pre-planned postoperative ICU admission) or on admission to SICU after non-cardiac surgery (both elective, urgency and emergency cases). If predictive score of postoperative delirium is more than 115 and meet all inclusion criteria without any exclusion criteria, researcher provides information about study objective, procedure, and benefit from participation in the study to the patients and/or proxies in order to obtain informed consent (at ward during pre-anesthesia evaluation or at SICU counseling room before SICU admission).

### Consent

Once patient has been screened and confirmed by investigators, the patient, or proxy (legally authorized representatives) is approached for informed consent. The investigators discuss the trial and ensure that the patient understands the material and given time to review the material and ask any questions. The patient is enrolled into the study only after informed consent is obtained.

### Randomization

Recruited patients are randomized 1:1 (computer generated number) to receive either (1) nocturnal dexmedetomidine (9 pm – 6 am) during ICU stay starting from postoperative day 0 (DEX group) or (2) placebo (P group).

### Blinding

All study medications are locally prepared by one of the investigators in the pharmacy room to ensure that bedside nurses received identical-looking 50-ml infusion bags containing either 0.9% NaCl or dexmedetomidine 200 µg in 50 ml of 0.9% NaCl (4 µg/ml). The blinded assessors are completing outcome assessments.

### Intervention

At 9:00 pm, all current sedatives (i.e., propofol, lorazepam, or midazolam) are halved, and nocturnal (9:00 pm to 6:00 am) intravenous dexmedetomidine 0.1 µg/kg/h (based on subject's calculated ideal body weight rounded down to nearest multiple of 5 kg) or equivalent ml/h of 0.9% NaCl is administered to the patient. The study drug infusion is halved at 5:45 am and discontinued at 6:00 am.

The targeted sedation goal during nocturnal study period is RASS of -1. The study drug infusion rate is increased by 0.1 µg /kg/h (or equivalent ml/h in placebo group) every 15 minutes when RASS score is greater than or equal to 0 up to maximum rate of 0.7 µg /kg/h, until target RASS is achieved. The study drug infusion rate is decreased by 0.1 µg /kg/h (or equivalent ml/h in placebo group) every 15 minutes when RASS score is less than or equal to -2. Nocturnal dexmedetomidine and equivalent ml/h of 0.9% NaCl placebo are administered continuously until patient is discharged from ICU. All analgesic and sedative therapy choices are left to discretion of bedside clinician.

If agitation occurs (i.e., RASS ≥ + 2), study medication (either dexmedetomidine or placebo) is titrated upward. If maximum rate is reached and agitation persists, bolus intravenous propofol or increased propofol infusion rate (based on discretion of bedside clinician) at minimum effective dose can be titrated upward if hemodynamically tolerable/not exceed 4 mg/kg/h.

Non-pharmacologic prevention/intervention of postoperative delirium including reorientation, non-pharmacologic sleep protocol, getting patient out of bed and walking, encouraging use of eyeglasses and hearing aids, encouraging fluid intake, proactive geriatric consultation, reducing opioid use, and discontinuing standing orders for sleeping pills are implemented equally in both groups.

Delirium assessment is performed by using Thai CAM-ICU twice daily (7 am, 7 pm). Assessment begins on post-operative day 1 and continues until ICU discharge or for 7 days (if ICU stay is longer) or death. Patient with delirium is further assessed until CAM-ICU negative for 24 hours. Pain assessment is performed in concomitant with delirium assessment.

Data collection begins on first day of ICU admission and continues until ICU discharge or 7 days (if ICU stay is longer) or death. Some data are collected by chart review.

Consort diagram giving the flow of participants throughout the study is showed in Figure 1.

### Rescue Therapy

All patients in this study are received non-pharmacologic prevention/ intervention of postoperative delirium (mentioned in intervention section).

If hyperactive delirium with significant symptoms occurs, haloperidol 0.5 – 2.5 mg is administered intramuscularly/intravenously and can be titrated every 30 minutes if symptoms persist (maximum dose: 10 mg/day). If oral medications are allowed, 12.5 – 25 mg of quetiapine can be administered (maximum dose: 75 mg/day). If agitation persists despite following treatment, intravenous propofol bolus or continuous drip is permitted. Psychiatric (in patient with 65 years of age or younger) or geriatric (in patient with 65 years of age or older) consultation is permitted if haloperidol use > 5 mg/day and/or quetiapine use > 50 mg/day. All rescue therapy types, route of administration and dosage are based on discretion of bedside physician. Benzodiazepines are allowed as an intermittent bolus in case patient's symptoms persists despite receiving medications listed in rescue therapy. Other rescue medications are also allowed depending on attending physician's discretion.

### Adverse Events

Patient's heart rate is monitored continuously as per ICU standard. Blood pressure is monitored hourly if non-invasive blood pressure is used or continuously if arterial line catheter is placed. Unexpected serious adverse events are recorded from the time of randomization until ICU discharge or day 7 or death, whichever comes first.

### Outcome Measurement

#### Primary outcomes

1. Incidence of delirium
2. Others: delirium outcomes: delirium-free days, onset of first delirium, incidence of subsyndromal delirium

#### Secondary outcomes

1. Adverse effects from dexmedetomidine: hypotension, bradycardia
2. Secondary delirium-related outcomes: episodes of nosocomial infection, duration of mechanical ventilation, ICU length of stay (ICU-LOS), duration of hospital stay, ICU-mortality, in-hospital mortality, 28-day mortality

#### Exploratory outcomes

1. Medication outcome: amount of sedative and an analgesic drug administered.
2. Factor associated with 28-day mortality.

### Timeline

Study timeline. (Figure 2)

## DATA ANALYSIS PLAN

### Sample size calculation

Primary outcome is the incidence of postoperative delirium between two groups (patients receive nocturnal dexmedetomidine or placebo after surgery). From Y. Skrobik, et al. study "Low-Dose Nocturnal Dexmedetomidine Prevents ICU Delirium A Randomized, Placebo-controlled Trial", the incidence of ICU delirium in patients receiving nocturnal dexmedetomidine was 20% and the placebo group was 46%.[11] The output of the sample size calculation from n4Studies. Two independent proportions formula with ratio = 1. All analyses follow the intention-to-treat principle. 80% power is used. A two-tailed p-value < 0.05 is considered statistically significant.

The sample size needed for each group is 51. If dropout rate is 10%, the sample size is 56.66 ≈ 57 in each group.

## OUTCOME ANALYSIS PLAN

### Statistical analysis

Demographic and clinical variables are summarized using descriptive statistics. Continuous variables are described as mean and SD or median and interquartile ranges (IQRs) depending on data distribution. Categorical variables are described as frequencies, proportion and 95% confidence interval (CI). Comparison between intervention and placebo group is by independent t-test or Mann-Whitney U test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. Risk of delirium-associated death at 28 days after surgery is calculated using multiple Cox regression hazards model and presented as hazard ratio (HR) and 95% CI and adjusted HR and 95% CI. Kaplan-Meier survival curves are generated and then compared using log-rank tests. All tests are 2-tailed with p value of less than 0.05 considered statistically significant. Intention to treat analysis is used to analyze all data. PASW Statistics v.18 is used for statistical analysis.

## DATA MANAGEMENT AND DATA MONITORING

### Input data and monitoring method

- Baseline patient characteristics variables (Table 1)
- Intraoperative variables (Table 2)
- ICU-related variables (Table 3)
- Primary and secondary outcomes monitoring method and timing – all performed by blinded assessors (Table 4)
- Medication outcomes monitoring method and timing – all performed by blinded assessors (Table 5)

### Definition of Variables

- Delirium is defined as having feature 1 and feature 2 and either feature 3 or 4 according to Confusion Assessment Method-Intensive Care Unit (CAM-ICU)
- Hypotension is defined as any documented systolic blood pressure below 90 mmHg or required treatment

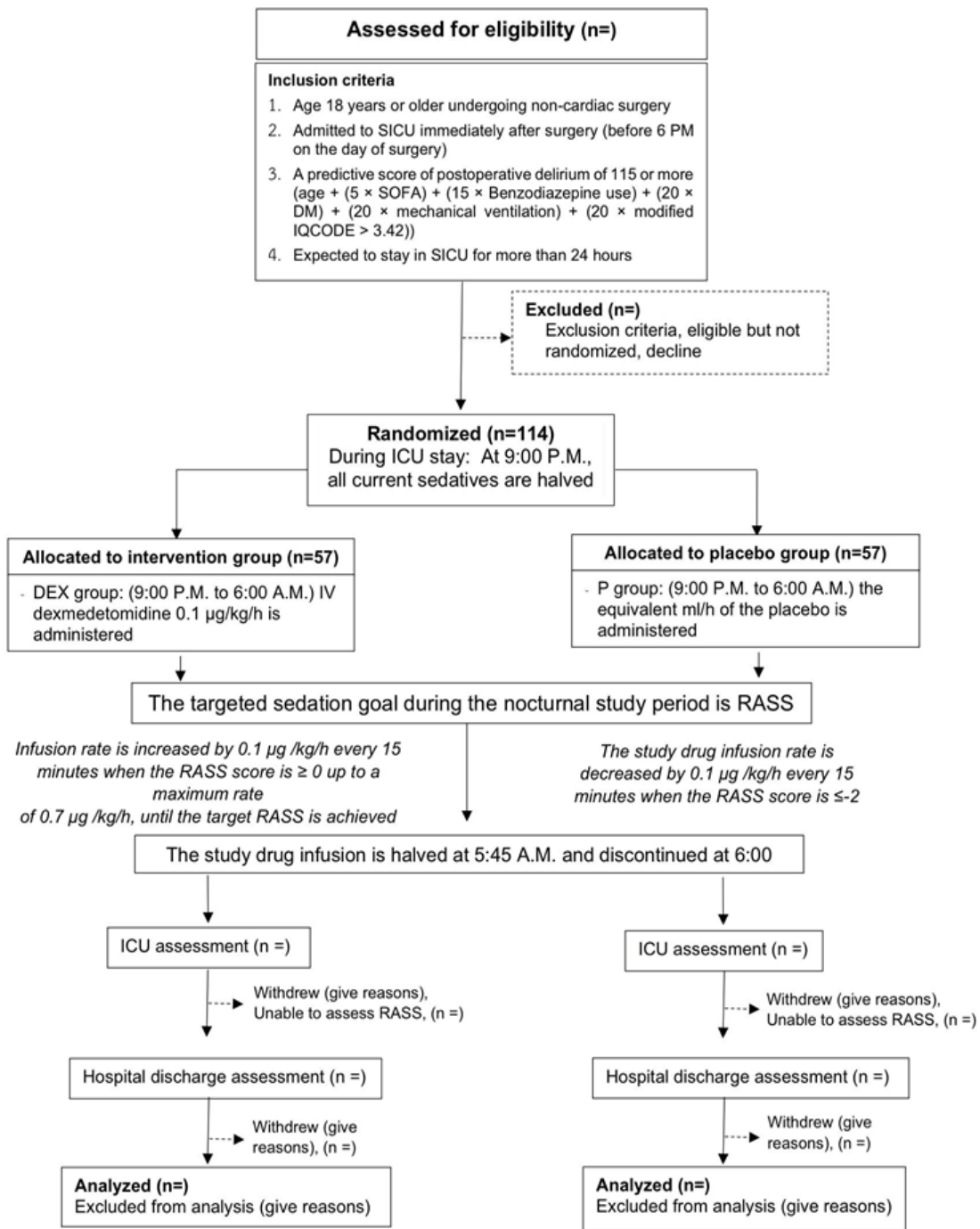


Figure 1. Consort diagram giving the flow of participants throughout the study.

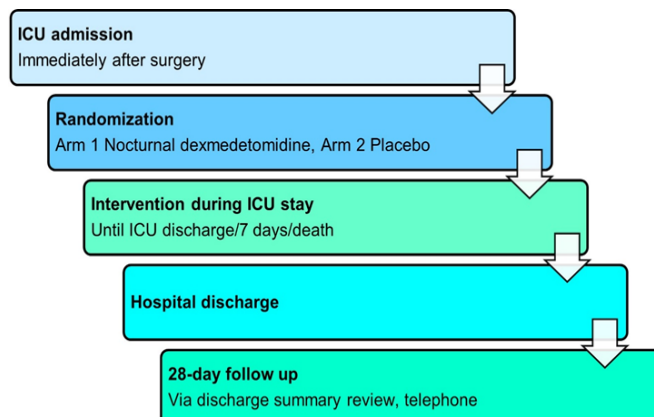


Figure 2. Study timeline.

- Bradycardia is defined as any documented heart rate below 50 beats per minute.

### Research Instruments

Predictive scores of POD in critically ill surgical patients is used for screening patients. A predictive score of POD in critically ill surgical patient is (age + (5 × SOFA) + (15 × Benzodiazepine use) + (20 × DM) + (20 × mechanical ventilation) + (20 × modified IQCODE > 3.42)) with the cut point of 115.[8]

Thai version of Confusion Assessment Method Intensive Care Unit (CAM-ICU) is used for assessment of delirium. The CAM-ICU is worldwide used for assessment of delirium in critically ill patients and has demonstrated pooled sensitivity of 80%, pooled specificity of 95.9%, and pooled area

under summary receiver operating characteristic curve (AUC) of 0.97.[3] CAM-ICU comprises 4 features which assess the following: acute change or fluctuation of mental status (feature 1), inattention (feature 2), altered level of consciousness (feature 3), and disorganized thinking (feature 4).[12] The Thai version of CAM-ICU has been established validity and reliability with sensitivity of 92.3%, specificity of 94.7%, and inter-rater reliability (Cohen's  $\kappa$  = 0.81).[13]

Confusion Assessment Method-Intensive Care Unit (CAM-ICU) 7 is also used for assessment severity of delirium. CAM-ICU-7 showed high internal consistency (Cronbach's alpha=0.85) and good correlation with DRS-R-98 scores (correlation coefficient=0.64).

**Table 1.** Baseline patient characteristics variables.

Baseline patient characteristics – collected at enrollment	Collection method
Age/Sex	Chart review
APACHE-II score <sup>a</sup> , SOFA score <sup>b</sup>	Chart review
Modified IQCODE <sup>c</sup>	Proxy interview
Predictive score of postoperative delirium	Chart review, proxy interview
Comorbidities	
- Hypertension	
- Diabetes mellitus	
- Smoking	
- Alcohol use (≥2 drinks/ day)	
- Drug abuse	
- Depression	
- Heart failure	
- COPD	
- Neurodegenerative disease	
- CKD	
- Liver disease	
- Cancer	Chart review
Sedative at randomization	Chart review
Type of pain control	Chart review
RASS <sup>d</sup> at randomization	Chart review

<sup>a</sup> APACHE-II score: Acute Physiology and Chronic Health Evaluation score

<sup>b</sup> SOFA score: Sequential Organ Failure Assessment score

<sup>c</sup> Modified IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly

<sup>d</sup> RASS: Richmond Agitation-Sedation Scale

**Table 2.** Intraoperative variables.

Intraoperative variables – collected at enrollment	Collection method
Site of surgery	Chart review
- Intra-abdominal surgery	Chart review
- Orthopedic surgery (extremities)	Proxy interview
- ENT surgery	Chart review, proxy interview
- Gynecologic surgery	
- Vascular surgery	
- Urologic surgery	
- Spine surgery	
- Other	Chart review

**Table 2. (Continued)** Intraoperative variables.

Intraoperative variables – collected at enrollment	Collection method
Type of surgery	
- Emergency	
- Elective	Chart review
Intraoperative blood loss, ml, mean $\pm$ SD	Chart review
Operation time, min, mean $\pm$ SD	Chart review
Total fluid intake, ml	Chart review
Intraoperative events	
- Hypotension	Chart review
- Hypoxemia	Chart review
- Hypoglycemia	Chart review
- Hyperglycemia	Chart review

<sup>a</sup>ENT surgery: Ears, Nose, Throat surgery

**Table 3.** ICU-related variables.

ICU-related variables	Collection method
Coma $\geq$ 1 h	Chart review
Deeper sedation (RASS $\leq$ -2) $\geq$ 1 h	Chart review
Early mobilization (<24 h after surgery)	Chart review
Maximum pain level	Chart review
Predominant mode of mechanical ventilation	Chart review
- Require ventilation	
- Assist/Control	
- IMVa	
- Spontaneous	
- Other	
- No ventilation	Chart review
Presence of infection	Chart review
Presence of shock	Chart review

<sup>a</sup>IMV: Intermittent mandatory ventilation

**Table 4.** Primary and secondary outcomes monitoring method and timing – all performed by blinded assessors.

	Monitoring method	Timing
<b>Primary outcomes</b>		
Incidence of delirium	CAM-ICU <sup>a</sup>	8 am and 8 pm throughout ICU stays
Other delirium outcomes		
- Delirium-free days		
- Onset of first delirium		
- Subsyndromal delirium		
<b>Secondary outcomes</b>		
Adverse events from dexmedetomidine	Standard ICU vital signs monitoring	Continuous monitoring during drug infusion
- Hypotension		
- Bradycardia		
Secondary delirium-related ICU outcomes	Chart review	At ICU discharge
- Episodes of nosocomial infection		
- Duration of mechanical ventilation		
- ICU length of stay		
- ICU-mortality		

**Table 4. (Continued)** Primary and secondary outcomes monitoring method and timing – all performed by blinded assessors.

	Monitoring method	Timing
- Length of hospital stay	Chart review	At hospital discharge
- In-hospital mortality		
- 28-day mortality	Discharge summary review, Telephone	28-day follow up period

<sup>a</sup> CAM-ICU: Confusion Assessment Method-Intensive Care Unit

**Table 5.** Medication outcomes monitoring method and timing – all performed by blinded assessors.

	Monitoring method	Timing
<b>Study medications</b>		
- Maximum infusion rate, ml/h	ICU medication record	ICU discharge
- Average infusion rate, ml/h		
- Maximum dose, µg/kg/h		
- Average dose, µg/kg/h		
<b>Other ICU medications</b>		
Propofol (IV)	ICU medication record	ICU discharge
Midazolam (any route)	ICU medication record	ICU discharge
Fentanyl (IV)	ICU medication record	ICU discharge
Steroid use (any route)	ICU medication record	ICU discharge
Antipsychotic use (any route)	ICU medication record	ICU discharge
Oral analgesic use	ICU medication record	ICU discharge

Known-groups validity was supported by separation of mechanically ventilated and non-ventilated assessments. Median CAM-ICU-7 scores demonstrated good predictive validity with higher odds (OR=1.47; 95% CI=1.30-1.66) of in-hospital mortality, and lower odds (OR=0.8; 95% CI=0.72-0.9) of being discharged home after adjusting for age, race, gender, severity of illness, and chronic comorbidities.[14]

Richmond Agitation Sedation Scale (RASS) is used for assessment of consciousness level. It comprises 10-point scale ranging from -4 to +5, with RASS score of 0 indicating calm and alert patient. Positive RASS score indicates agitation or aggressive symptom ranging from +1 (mild rest - restlessness) to +4 (dangerous agitation). Negative RASS score indicates drowsy, stupor or coma differentiated by response to verbal command (score -1 to -3) and response to physical stimulation (score -4) and no response (score -5).

Thai version of modified Informant Questionnaire on Cognitive Decline in the Elderly (modified IQCODE) is used for assessment of dementia by asking patient's caregivers. The questionnaire contains 32 items with scores ranging from 1 to 5. Average score of more than 3.42 has 90%, 95% and 92% sensitivity, specificity, and accuracy for dementia respectively.[15]

Acute Physiology and Chronic Health Evaluation II (APACHE II) is used for assessment of disease severity on admission, containing 3 sections: 12 physiologic variables to assess degree of acute illness, age, and chronic health status. Age and chronic health status are weighted according to their relative impact. Higher score indicates more severe disease.

Sequential Organ Failure Assessment score (SOFA score) is used for assessment of organ dysfunction during ICU ad-

mission by evaluating 6 organ systems (respiratory, cardiovascular, hepatic, renal, central nervous system, and coagulation). Variables representing each system are scored from 1 to 4. Higher score indicates higher severity.[16]

Numeric Rating Scale (NRS) is for assessment of pain. A card containing number 0 to 10, in 1 cm. interval, along the line. A scale of "0" indicates no pain while "10" indicates the most severe pain.

Critical Care Pain Observation Tool (CPOT) is used for assessment of pain during ICU admission (in case NRS cannot be used) by evaluating 4 behavioral domains (facial expressions, body movement, muscle tension, and compliance) with ventilator for intubated patient or vocalization for non-intubated patient. Each CPOT domain consists of three descriptions of patient's state or behavior, with the first describing the mildest level with a score of 0, and the third describing the most severe level with a score of 2. CPOT score ranges from 0 (no pain) to 8 (sever pain).[17]

## DISCUSSION

We conduct the trial to compare use of nocturnal dexmedetomidine infusion versus placebo (0.9% normal saline), in critically ill surgical patients, with high risk of POD, admitted to SICUs after non-cardiac surgery. Although previous published studies demonstrated that nocturnal dexmedetomidine infusion could reduce occurrence of POD in SICUs patients, they did not focus on patients who had high risk for POD.[10-11] Since dexmedetomidine's availability is considerably more limited than other sedative agents in our setting, we are interested in using nocturnal dexmedetomidine to prevent development of POD only in



high-risk critically ill surgical patients. We identify high-risk patients by using the previously developed predictive score from our institution. The predictive score is “age + (5 × SOFA (Sequential Organ Failure Assessment) score) + (15 × Benzodiazepine use) + (20 × having diabetes mellitus) + (20 × on mechanical ventilation) + (20 × having modified IQCODE (Modified Informant Questionnaire on Cognitive Decline in the Elderly) > 3.42)”. [8] We then validate this predictive score both in our institution and other two academic hospitals. The validation shows the area under receiver operating characteristic curve (AUROC) of 0.83. Optimum cutoff value to discriminate between a high and low probability of postoperative delirium in SICU patients is 115. This cutoff offers the highest value for Youden’s index (0.50), the best AUROC, and the optimum value for sensitivity (78.9%) and specificity (70.9%). The validation study is in process of submission for publication (TCTR20180105001). If this hypothesis is proven effective, nocturnal dexmedetomidine infusion in high-risk patients would have potential to improve ICU care, because POD leads to higher morbidities, prolonged mechanical ventilation, ICU stays and mortalities. [4–6]

**Study strength:** this is the first randomized controlled trial to study effect of nocturnal dexmedetomidine to prevent POD exclusively in high-risk critically ill surgical patients. The protocol is clear and reproducible, while the assessors and patients remain blinded throughout the study.

**Limitations of the study** are inability to apply to medical ICU settings, and low risk of postoperative delirium surgical patients. Also, COVID-19 pandemic has impeded enrollment of patients due to decrease in operating room capacity in our hospital.

## ETHICS

The study sponsor is Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand, which takes no part in design, conduct, analysis, review or approval of manuscript. We continuously review evolving scientific literature and evidence, related to the safety of the study over trial duration. The trial receives ethic approval from Siriraj Institutional Review Board (SIRB Protocol No. 919/2563 (IRB3), COA No. Si 041/2021) and the enrollment has begun.

## CONFIDENTIALITY

Informed consents are obtained at ICU/ward prepared counseling room. Code is used and recorded instead of patient’s name/hospital number/admission number. Date of birth, initials of name - surname or other personal information are not collected. This study’s data are recorded only in research record form and password protected in investigators’ personal computers. When the study is concluded, data/documents recorded in physical form (paper) would be destroyed as per destruction of document policy of Siriraj Hospital, and data/documents recorded in digital form will be permanently deleted from all investigators’ computers.

## DISSEMINATION POLICY

When the study is concluded, we plan to disseminate the results in peer-reviewed critical care medicine or anesthesiology related journals, conferences nationally and internationally.

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## AUTHORS’ CONTRIBUTIONS

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- Funding acquisition: Onuma Chaiwat
- Methodology: Raksakul Kuanha, Thanus Teerattitayang-gool, Onuma Chaiwat, Annop Piriypassom, Nuanprae Kitisin, Napat Thikom
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## SUPPLEMENTARY MATERIALS

none

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