Protocol

DESIRe trial

(DExmedetomidine for Sepsis in ICU Randomized Eavaluation trial)

Effect of dexmedetomidine on survival, duration of mechanical ventilation and multi-organ function in sepsis patients under lighter sedation: a randomized controlled trial

Final version

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Background

Dexmedetomidine, a highly selective arfa2-adrenergic agonist, is a unique sedative agent that causes less severe acute tolerance, drug addiction, and withdrawal symptoms compared with gamma-aminobutyrate agonists. Dexmedetomidine was approved for short-term intensive care unit (ICU) sedation in Japan in 2004, and it has particularly been used for surgical ICU patients. In August 2010, dexmedetomidine was approved in Japan for sedation lasting for more than 24 hours.

Recent evidence suggested that dexmedetomidine has organ protective effects including neuroprotection, cardioprotection, renal protection, maintenance of peristaltic motion, and anti-inflammatory action. Dexmedetomidine was shown to significantly decrease the infarct size in isolated rat hearts. Additionally, dexmedetomidine exhibited a preconditioning effect against ischemic injury in hippocampal slices, and this result was considered to be due to an apoptosis inhibitory effect of dexmedetomidine. Aydin C et al reported that dexmedetomidine enhanced the spontaneous contractions of the ileum in peritonitis rats, as compared with propofol and midazolam. Taniguchi and colleagues demonstrated that
dexmedetomidine reduced high mortality rates and the plasma cytokine concentrations of interleukin-6 and tumor necrosis factor alpha, in endotoxemic rats.

A meta-analysis demonstrated that the perioperative use of alfa2-adrenergic agonists, including dexmedetomidine infusion, decreased the number of cardiovascular events in patients undergoing cardiac surgery. Dexmedetomidine-treated patients undergoing thoracotomy showed an increase in urine output, reduction in serum creatinine levels, and reduced diuretics use in a randomized placebo-controlled double-blind study. Furthermore, septic patients receiving dexmedetomidine showed improved 28-day mortality rates as compared with septic patients receiving lorazepam in a sub-group analysis of a MENDS randomized controlled trial.

These positive effects of dexmedetomidine on the cardiovascular system, neurons, kidneys, gastrointestinal tract, and inflammation, are expected to improve mortality rates in septic patients. However, large clinical research studies have yet to be conducted. We designed and conducted the DESIRE trial (DEXmedetomidine for Sepsis in ICU Randomized Evaluation trial) to assess the hypothesis that dexmedetomidine may improve clinical outcome and exert these organ protective effects on septic patients.

**Objective**

To determine whether dexmedetomidine improves clinical outcome and exerts organ protective effects in septic patients.

**Eligibility**

1. **Inclusion criteria**

   Patients will be eligible if they are **20 years old or older adult ICU patients with sepsis who are considered to require mechanical ventilation for at least 24 hours.**

   a) The definition of sepsis will be systemic inflammatory response
syndrome (SIRS) due to an infection.

b) The definition of SIRS will be the presence at least two of the following four criteria: 1) fever (>38°C) or hypothermia (<36°C); 2) tachycardia (>90/min); 3) tachypnea (>20/min) or PaCO₂<32 Torr; and 4) leukocytosis (white blood cell [WBC] count>12000/mcl), leukopenia (WBC count<4000/mcl) or normal WBC count with >10% immature forms.

c) Patients will be enrolled if they have acute pancreatitis, but not burns and heat stroke.

2. Exclusion criteria

Patients will be excluded if they meet any of the following criteria: 1) Severe chronic liver disease (Child B or C); 2) acute myocardial infarction or heart failure (New York Heart Association 4); 3) drug dependence or alcoholism; 4) psychological illness or severe cognitive dysfunction; 5) pregnant or lactating women; 6) patients who are allergic to dexmedetomidine; and 7) attending physician's decision

Methods

1. Study design

We will perform an open-label, multicenter, randomized controlled trial with blinded-endpoint assessment.

2. Randomization

When an attending physician judges that a patient is eligible, they will obtain informed consent from the patient or the patient's family. Then they will register and randomize the patient online by accessing the Internet Data and Information Center for Medical Research (INDICE). INDICE is the internet-based medical research support system that was provided by the University hospital Medical Information Network (UMIN). The randomization process will use block randomization stratified by center, emergent surgery, soft-tissue infection, and chronic obstructive pulmonary disease dysfunction.
3. Administration of study medication

From the beginning of ICU treatment, we will sedate the patient by using dexmedetomidine (group A) or not (group B) in accordance with the “Sedation & analgesia protocol.”

Duration of sedation will be more than 24 hours.

As a general rule, we will not deviate the timing, dose and duration of the study drug from the protocol.

4. Outcome measures

Co-primary outcome measures:

a) 28-day mortality rate

The mortality rate of patients after 28 days.

b) Duration of mechanical ventilation

Originally, the duration of mechanical ventilation in the ICU, including non-invasive ventilation was defined as primary outcome. However, duration of mechanical ventilation was highly influenced by mortality. Therefore, we set 28-days ventilator free days as primary endpoint.

Secondary outcome measures:

a) Length of stay in the ICU

b) Length of stay in the hospital

c) Agitation and delirium

d) Cognitive function

e) Occurrence of arrhythmia or myocardial ischemia

ef) Renal function

Blood urea nitrogen (BUN), and creatinine levels, estimated glomerular filtration rate, daily urinary output, and requirement for renal replacement therapy will be used as indicators of renal function.

g) Treatment of infection
Duration of antimicrobial therapy will be assessed within the 28 days or until the day of discharge if patients are discharged earlier than 28 days.

fb) Inflammatory markers

Laboratory markers of inflammation, including C-reactive protein (CRP) and procalcitonin (PCT) will be measured on days 1, 43, 87, and 14.

gi) Organ failure control

The Sequential Organ Failure Assessment (SOFA) score will be used to quantify organ failure during ICU stay.

hj) Coagulopathy control

The Disseminated Intravascular Coagulation (DIC) score from the Japanese Association for Acute Medicine (JAAM) will be used to assess coagulopathy control during ICU stay.

ik) Nutrition control

The daily energy intake by enteral nutrition will be monitored.

jl) Sedation control

The doses of sedative drugs and analgesic drugs used during ICU stay will be recorded.

Adverse events

5. Criteria of weaning from mechanical ventilation

We will attempt to wean a patient from mechanical ventilation if the patient fulfills all of the following criteria:

a) Improvement or stabilization of underlying illness

b) PaO₂ >60 mmHg or SpO₂ >92% under FiO₂ 0.5 and PEEP <8cmH₂O

c) Normal PaCO₂ or less than premorbid PaCO₂ level

d) Sufficient spontaneous inspiration and Rapid-Shallow Breathing Index (RSBI) <100/L

e) We will use the spontaneous breathing trial or T-tube trial

e) An attending physician judges that the patient can be weaned from mechanical ventilation
6. Schedule of assessments

a) Assessment of pain, agitation and delirium

Pain will be assessed using the Visual Analogue Scale or the Behavioral Pain Scale if the patient is sedated deeply. Agitation and delirium will be assessed using the Richmond agitation-sedation scale and Confusion Assessment Method for ICU patients, respectively.

b) Cognitive function

Cognitive function will be evaluated using the Mini Mental State Examination on day 28 or on the day of discharge if a patient is discharged earlier than 28 days.

c) Monitoring of electrocardiogram

We will perform continuous electrocardiogram monitoring to detect fatal arrhythmias (bradycardia, ventricular fibrillation, or sinus arrest).

d) Laboratory tests

Laboratory tests will include complete blood cell count (WBC, hematocrit, and platelets), measurement of coagulation markers (prothrombin time—international normalized ratio, fibrin degradation products, and fibrinogen), chemical test (BUN, creatinine, total bilirubin, CRP and PCT), and a blood gas analysis (pH, PaCO₂, PaO₂, and HCO₃⁻).

e) Evaluation of organ failure and coagulopathy

Organ failure and coagulopathy will be evaluated using the SOFA score and DIC score by JAAM, respectively.

7. Withdrawal from the study

A patient will be withdrawn from the study for any of the following reasons:

a) Withdrawal of consent

b) Severe adverse events due to dexmedetomidine

c) Decision of main investigator or collaborator

8. Management of sepsis

We will treat the patients in accordance with The Japanese Guidelines for
9. Management of sedation and enteral feeding

We will sedate the patients in accordance with the “Sedation & analgesia protocol,” as stated above.

We will perform enteral feeding in accordance with the following criteria:

a) Enteral feeding will be used prior to parenteral feeding.

b) Enteral feeding will be performed as early as possible (e.g. within 48 hours).

c) The dose of enteral feeding will be gradually escalated to achieve the goal (25-30 kcal/kg/day).

d) The patient will be placed in a semi-recumbent position, with the head elevated 30-45 degrees, while enteral feeding occurs.

e) Continuous enteral feeding or nasojejunal feeding will be considered in patients with a high risk of aspiration or uncontrolled blood glucose.

f) Continuous small-volume enteral feeding will be implemented in cases of osmolar diarrhea. We will attempt to continue enteral feeding where possible.

10. Treatment following extubation

Following extubation, we will continue to treat the patients in accordance with The Japanese Guidelines for the Management of Sepsis by the Japanese Society of Intensive Care Medicine.

11. Data and safety monitoring board (DSMB) and interim analysis

The DSMB consists of Dr. Sadao Kawasaki (Department of Emergency Medicine, Minami Wakayama Medical Center, Japan), Dr. Takahiro Ashikawa (Department of emergency medicine, Minami Wakayama Medical Center, Japan) and Dr. Yasuhiro Iwasaki (Department of Emergency and Critical Care Medicine, Wakayama Medical University, Japan). The DSMB will independently perform an interim analysis one year after recruitment has started. If a serious adverse event occurs during this trial, the DSMB will decide whether to
continue the trial or not.

12. Predictable adverse events and emergent reporting system
Predictable adverse events due to dexmedetomidine include hypotension, hypertension, bradycardia, ventricular fibrillation, cardiac arrest, sinus arrest, hypoxemia and apnea.

If an unpredictable or a serious adverse event occurs, the attending physician will report the case to the DSMB. The attending physician will cease administration of dexmedetomidine if they consider dexmedetomidine to be harmful to the patient.

13. Case registration and data collection
We will perform case registration, randomization and data collection online by accessing the INDICE. All researchers will require an ID and a password when they input the data. For randomization, they will need to input the sex, age, emergent surgery and center of the patients.

A chief researcher of each center will store the list of randomization numbers and patient IDs securely (e.g. in the security box).

We will delete the collected data five years after reporting and publication of the results.

14. Planned study duration
The planned study duration will be five years after approval has been obtained from the Institutional Review Board of each hospital (three years for patient recruitment).

15. Statistical analysis
The DESIRE trial has been designed to compare the dexmedetomidine group with the control group. A two-sided P value of less than 0.05 will be considered to indicate a statistical significance.

The secondary outcomes of agitation, delirium, arrhythmia, cardiac ischemia, hospital acquired infection and renal replacement therapy will
be compared between the two groups using the chi-square test. The 28-day mortality rate, duration of mechanical ventilation, length of ICU stay and duration of hospital stay will be compared between the two groups using the log-rank test. Kaplan-Meier survival curves will be used for graphical presentation.

The Wilcoxon signed-rank test will be used to compare the outcomes of renal function, daily urinary output, duration of antimicrobial therapy, inflammatory markers (CRP and PCT), severity score (SOFA score and DIC score), duration of enteral nutrition, doses of other drugs, including sedatives, analgesics and psychoactive drugs, and cognitive function between two groups.

We will conduct the subgroup analysis for age (>or = 65 year-old, or< 65 year-old), severity score (APACHE II > or = median, or < median), site of infection (abdomen, thorax or others) and shock (cardiovascular SOFA subscore > or = 3, or < 3).

16. Sample size determination

Planned sample size: 200 cases

In the subgroup analysis of sepsis patients in the MENDS trial by Pandharipande PP et al., dexmedetomidine resulted in an increased 28-day survival rate (84% in the dexmedetomidine group versus 59% in the control group). From this, we have estimated that the 28-day survival rate will be 80% in the dexmedetomidine group and 60% in the control group. We have estimated that, with a sample size of 172 patients, the study will have 80% power to detect a significant difference using the log-rank test. We have estimated that the rate of dropout or withdrawal will be approximately 15%, and thus we plan to enroll 200 patients.

17. Estimated number of enrolled patients in Wakayama Medical University

We estimated to enroll approximately 25 patients per year.

18. Chief investigator and collaborator
Chief investigator:  
Yu Kawazoe, Division of Emergency and Critical Care Medicine, Tohoku University Hospital Emergency Center Department of Emergency and Critical Care Medicine, Wakayama Medical University, Japan  
1-1, Seiryo, Aoba, Sendai, Miyagi 980-0872, JAPAN  

Kyohei Miyamoto, Department of Emergency and Critical Care Medicine, Wakayama Medical University, Japan  
811-1, Kimiidera, Wakayama-City, Wakayama, 641-8509, JAPAN  

Collaborator:  
Takeshi Morimoto, Department of Clinical Epidemiology, Hyogo College of Medicine, Japan  
1-1, Mukogawa-Town, Nishinomiya-City, Hyogo, 663-8501, JAPAN  

Hitoshi Yamamura, Department of Disaster and Emergency Medicine, Hirosaki University Graduate School of Medicine Department of Trauma and Critical Care Medicine, Osaka City University Hospital, Japan  
5 Zaifu, Hirosaki, Aomori 036-85621-5-7, Asahicho, Osaka-City, Osaka, 545-8586, JAPAN  

Akihiro Fuke, Emergency and Urgent Medical Care Center, Osaka City General Hospital, Japan  
2-13-22, Miyakoijma-Hondori, Osaka-City, Osaka, 534-0021, JAPAN  

Atsunori Hashimoto, Department of Emergency and Critical Care Medicine, Hyogo College of Medicine, Japan  
1-1, Mukogawa-Town, Nishinomiya-City, Hyogo, 663-8501, JAPAN  

Makoto Ito, Department of Anesthesiology, Yamaguchi Grand Medical Center, Japan  
77, Osaki, Hofu-City, Yamaguchi, 747-8511, JAPAN
Nobuaki Shime, Department of Emergency Medicine, Critical Care, National Hospital Organization Kyoto Medical Center, Japan
1-1, Fukakusamukaihatacho, Kyoto-City, Kyoto, 612-8555, JAPAN

Kohei Kato, Department of Emergency Medicine, Sapporo Medical University, Japan
16-291, Minamiichijonishi, Sapporo-City, Hokkaido, 060-8543, JAPAN

Kenji Yamauchi, Shimane University Hospital, Japan
89-1, Ennya-Town, Izumo-City, Shimane, 693-8501, JAPAN

Hiroyuki Koami, Saga University Hospital, Japan
5-1-1, Nabeshima, Saga-City, Saga, 849-8501, JAPAN
<table>
<thead>
<tr>
<th>Dates</th>
<th>Changes</th>
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<tbody>
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<td>24 July 2012</td>
<td>Protocol version 1 was fixed</td>
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<td>22 Oct 2013</td>
<td>We will conduct the subgroup analysis for age (less than 65 years-old or not), severity score (lower than the mean of APACHE II or not), site of infection (abdomen, thorax or not) and with or without circulatory failure (less than 3 point of cardiovascular SOFA subscore or not). We will conduct the subgroup analysis for age, sex, the higher or lower severity score, site of infection, with or without organ failure.</td>
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<td>8 April 2014</td>
<td>We added Kyohei Miyamoto (Wakayama Medical University) to Chief investigator.</td>
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<td>We changed affiliation of Takeshi Morimoto, from Kinki University Faculty of Medicine to Hyogo College of Medicine.</td>
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<tr>
<td>1 Apr 2015</td>
<td>We changed affiliation of Hitoshi Yamamura, from Osaka City University Hospital to Hirosaki University Graduate School of Medicine.</td>
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<tr>
<td>2 May 2015</td>
<td>We set 28-days ventilator free days as primary outcome instead of the duration of mechanical ventilation in the ICU, because duration of mechanical ventilation was highly influenced by mortality.</td>
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**Formatted Table**
1 Sep 2015  | We changed affiliation of Yu Kawazoe, from Wakayama Medical University to Tohoku University Hospital Emergency Center.

### Amendment

24 July 2012: The first edition enactment

28 Feb 2013: The following issues were decided in the DESIRE trial meeting

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