

Protocol

DESIRE trial

(DEXmedetomidine for Sepsis in ICU Randomized Evaluation 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

2015/9/1

Background

Dexmedetomidine, a highly selective α_2 -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

31 dexmedetomidine reduced high mortality rates and the plasma cytokine
32 concentrations of interleukin-6 and tumor necrosis factor alpha, in
33 endotoxemic rats.

34

35 A meta-analysis demonstrated that the perioperative use of
36 alfa2-adrenergic agonists, including dexmedetomidine infusion, decreased
37 the number of cardiovascular events in patients undergoing cardiac surgery.
38 Dexmedetomidine-treated patients undergoing thoracotomy showed an
39 increase in urine output, reduction in serum creatinine levels, and reduced
40 diuretics use in a randomized placebo-controlled double-blind study.
41 Furthermore, septic patients receiving dexmedetomidine showed improved
42 28-day mortality rates as compared with septic patients receiving lorazepam
43 in a sub-group analysis of a MENDS randomized controlled trial.

44

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

52

53 **Objective**

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

56

57 **Eligibility**

58 1. Inclusion criteria

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

62 a) The definition of sepsis will be systemic inflammatory response

63 syndrome (SIRS) due to an infection.

64 b) The definition of SIRS will be the presence at least two of the
65 following four criteria: 1) fever ($>38^{\circ}\text{C}$) or hypothermia ($<36^{\circ}\text{C}$); 2)
66 tachycardia ($>90/\text{min}$); 3) tachypnea ($>20/\text{min}$) or $\text{PaCO}_2 < 32$ Torr; and 4)
67 leukocytosis (white blood cell [WBC] count $>12000/\text{mcl}$), leukopenia (WBC
68 count $<4000/\text{mcl}$) or normal WBC count with $>10\%$ immature forms.

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

71

72 2. Exclusion criteria

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

79

80 **Methods**

81 1. Study design

82 We will perform an open-label, multicenter, randomized controlled trial
83 [with blinded-endpoint assessment](#).

84

85 2. Randomization

86 When an attending physician judges that a patient is eligible, they will
87 obtain informed consent from the patient or the patient's family. Then they
88 will register and randomize the patient online by accessing the Internet
89 Data and Information Center for Medical Research (INDICE). INDICE is the
90 internet-based medical research support system that was provided by the
91 University hospital Medical Information Network (UMIN). The randomization
92 process will use block randomization stratified by center, emergent surgery,
93 soft-tissue infection, and chronic [obstructive](#) pulmonary
94 [diseasedysfunction](#).

95

96 3. Administration of study medication

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

100 Duration of sedation will be more than 24 hours.

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

103

104 4. Outcome measures

105 Co-pPrimary outcome measures:

106 a) 28-day mortality rate

107 The mortality rate of patients after 28 days.

108 b) ~~Duration of mechanical ventilation~~28-day ventilator free days

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

113 ~~The duration of mechanical ventilation in the ICU, including non-invasive~~
114 ~~ventilation.~~

115

116 Secondary outcome measures:

117 a) Length of stay in the ICU

118 b) Length of stay in the hospital

119 c) Agitation and delirium

120 d) Cognitive function

121 ~~e) Occurrence of arrhythmia or myocardial ischemia~~

122 ~~e~~f) Renal function

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

126 ~~g) Treatment of infection~~

127 | ~~Duration of antimicrobial therapy will be assessed within the 28 days or~~
128 | ~~until the day of discharge if patients are discharged earlier than 28 days.~~

129 | f) Inflammatory markers

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

132 | g) Organ failure control

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

135 | h) Coagulopathy control

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

139 | i) Nutrition control

140 | The daily energy intake by enteral nutrition will be monitored.

141 | j) Sedation control

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

144 |

145 | Adverse events

146 | a) Occurrence of arrhythmia or myocardial ischemia

147 |

148 | 5. Criteria of weaning from mechanical ventilation

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

151 | a) Improvement or stabilization of underlying illness

152 | b) $PaO_2 > 60$ mmHg or $SpO_2 > 92\%$ under $FiO_2 0.5$ and $PEEP < 8$ cmH₂O

153 | c) Normal $PaCO_2$ or less than pre-morbid $PaCO_2$ level

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

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

157 | e) An attending physician judges that the patient can be weaned from
158 | mechanical ventilation

159

160 6. Schedule of assessments

161 a) Assessment of pain, agitation and delirium

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

166 b) Cognitive function

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

170 c) Monitoring of electrocardiogram

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

173 d) Laboratory tests

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

179 e) Evaluation of organ failure and coagulopathy

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

182

183 7. Withdrawal from the study

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

185 a) Withdrawal of consent

186 b) Severe adverse events due to dexmedetomidine

187 c) Decision of main investigator or collaborator

188

189 8. Management of sepsis

190 We will treat the patients in accordance with The Japanese Guidelines for

191 the Management of Sepsis by the Japanese Society of Intensive Care Medicine.

192

193 9. Management of sedation and enteral feeding

194 We will sedate the patients in accordance with the "Sedation & analgesia
195 protocol," as stated above.

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

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

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

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

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

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

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

209

210 10. Treatment following extubation

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

214

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

216 The DSMB consists of Dr. Sadao Kawasaki (Department of Emergency Medicine,
217 Minami Wakayama Medical Center, Japan), Dr. Takahiro Ashikawa (Department
218 of emergency medicine, Minami Wakayama Medical Center, Japan) and Dr.
219 Yasuhiro Iwasaki (Department of Emergency and Critical Care Medicine,
220 Wakayama Medical University, Japan). The DSMB will independently perform
221 an interim analysis one year after recruitment has started. If a serious
222 adverse event occurs during this trial, the DSMB will decide whether to

223 continue the trial or not.

224

225 12. Predictable adverse events and emergent reporting system

226 Predictable adverse events due to dexmedetomidine include hypotension,
227 hypertension, bradycardia, ventricular fibrillation, cardiac arrest,
228 sinus arrest, hypoxemia and apnea.

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

233

234 13. Case registration and data collection

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

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

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

243

244 14. Planned study duration

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

248

249 15. Statistical analysis

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

253 The secondary outcomes of agitation, delirium, arrhythmia, cardiac
254 ischemia, hospital acquired infection and renal replacement therapy will

255 be compared between the two groups using the chi-square test.

256 The 28-day mortality rate, duration of mechanical ventilation, length of
257 ICU stay and duration of hospital stay will be compared between the two
258 groups using the log-rank test. Kaplan-Meier survival curves will be used
259 for graphical presentation.

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

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

270

271 16. Sample size determination

272 Planned sample size: 200 cases

273 In the subgroup analysis of sepsis patients in the MENDS trial by
274 Pandharipande PP et al., dexmedetomidine resulted in an increased 28-day
275 survival rate (84% in the dexmedetomidine group versus 59% in the control
276 group). From this, we have estimated that the 28-day survival rate will
277 be 80% in the dexmedetomidine group and 60% in the control group. We have
278 estimated that, with a sample size of 172 patients, the study will have
279 80% power to detect a significant difference using the log-rank test. We
280 have estimated that the rate of dropout or withdrawal will be approximately
281 15%, and thus we plan to enroll 200 patients.

282

283 17. Estimated number of enrolled patients in Wakayama Medical University

284 We estimated to enroll approximately 25 patients per year.

285

286 18. Chief investigator and collaborator

287 Chief investigator:

288 Yu Kawazoe, [Division of Emergency and Critical Care Medicine,](#)
289 [Tohoku University Hospital Emergency Center](#)~~Department of Emergency and~~
290 ~~Critical Care Medicine, Wakayama Medical University,~~ Japan
291 [1-1, Seiryō, Aoba, Sendai, Miyagi 980-0872, JAPAN](#)

292 Kyohei Miyamoto, Department of Emergency and Critical Care
293 Medicine, Wakayama Medical University, Japan
294 811-1, Kimiidera, Wakayama-City, Wakayama, 641-8509, JAPAN

295
296 Collaborator:

297 Takeshi Morimoto, Department of Clinical Epidemiology, Hyogo
298 College of Medicine, Japan
299 1-1, Mukogawa-Town, Nishinomiya-City, Hyogo, 663-8501, JAPAN

300
301 Hitoshi Yamamura, [Department of Disaster and Emergency Meidicine,](#)
302 [Hirosaki University Graduate School of Medicine](#)~~Department of Trauma and~~
303 ~~Critical Care Medicine, Osaka City University Hospital,~~ Japan
304 [5 Zaifu, Hirosaki, Aomori 036-85621-5-7, Asahicho, Osaka-City,](#)
305 ~~Osaka, 545-8586,~~ JAPAN

306
307 Akihiro Fuke, Emergency and Urgent Medical Care Center, Osaka City
308 General Hospital, Japan
309 2-13-22, Miyakojima-Hondori, Osaka-City, Osaka, 534-0021, JAPAN

310
311 Atsunori Hashimoto, Department of Emergency and Critical Care
312 Medicine, Hyogo College of Medicine, Japan
313 1-1, Mukogawa-Town, Nishinomiya-City, Hyogo, 663-8501, JAPAN

314
315 Makoto Ito, Department of Anesthesiology, Yamaguchi Grand Medical
316 Center, Japan
317 77, Osaki, Hofu-City, Yamaguchi, 747-8511, JAPAN

318

319 Nobuaki Shime, Department of Emergency Medicine, Critical Care,
320 National Hospital Organization Kyoto Medical Center, Japan
321 1-1, Fukakusamukaihatacho, Kyoto-City, Kyoto, 612-8555, JAPAN

322

323 Kohei Kato, Department of Emergency Medicine, Sapporo Medical
324 University, Japan

325 16-291, Minamiichijonishi, Sapporo-City, Hokkaido, 060-8543,
326 JAPAN

327

328 Kenji Yamauchi, Shimane University Hospital, Japan
329 89-1, Ennya-Town, Izumo-City, Shimane, 693-8501, JAPAN

330

331 Hiroyuki Koami, Saga University Hospital, Japan
332 5-1-1, Nabeshima, Saga-City, Saga, 849-8501, JAPAN

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History of Change

<u>Dates</u>	<u>Changes</u>
<u>24 July 2012</u>	<u>Protocol version 1 was fixed</u>
<u>28 Feb 2013</u>	<u>—In the DEX group, we have to continue dexmedetomidine during the mechanical ventilation, but we can stop dexmedetomidine temporarily because of the severe circulatory failure.</u> <u>—The definition of weaning from mechanical ventilation was to be free from mechanical ventilation more than 24 hours.</u> <u>—The time of decision to be withdrawing from any treatment was regarded to termination of this study.</u>
<u>22 Oct 2013</u>	<u>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.</u>
<u>8 April 2014</u>	<u>—We added Kyohei Miyamoto (Wakayama Medical University) to Chief investigator.</u> <u>—We changed affiliation of Takeshi Morimoto, from Kinki University Faculty of Medicine to Hyogo College of Medicine.</u>
<u>1 Apr 2015</u>	<u>We changed affiliation of Hitoshi Yamamura, from Osaka City University Hospital to Hirosaki University Graduate School of Medicine.</u>
<u>2 May 2015</u>	<u>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.</u>

Formatted Table

1 Sep 2015

~~—We changed affiliation of Yu Kawazoe, from Wakayama Medical University to Tohoku University Hospital Emergency Center.~~

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338 Amendment

339 ~~24 July 2012: The first edition enactment~~

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341 ~~28 Feb 2013: The following issues were decided in the DESIRE trial meeting~~

342 ~~—In the DEX group, we have to continue dexmedetomidine during the~~

343 ~~mechanical ventilation, but we can stop dexmedetomidine temporally because~~

344 ~~of the severe circulatory failure.~~

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356 ~~investigator.~~

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