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**DExmedetomidine for Sepsis in ICU
Randomized Evaluation Trial
DESIRE Trial**

Statistical Analysis Plan

Japanese Version (Ver.1.0) 2016/3/17

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Study Statistician

26 **Aim of the study**

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

29

30 **End Points**

31 *Co-primary outcome measures*

32

33 28-day mortality rate

34 The mortality rate of patients after 28 days.

35 28-day ventilator free days

36 Originally, the duration of mechanical ventilation in the
37 ICU, including non-invasive ventilation were defined.

38 However, duration of mechanical ventilation was highly
39 influenced by mortality. Therefore, we set 28-days
40 ventilator free days as primary endpoint

41 28-days ventilator free days = 28 or days alive – days
42 under mechanical ventilation

43

44 *Secondary outcome measures*

45

46 a) Length of stay in the ICU

47 b) Length of hospital stay

48 c) Agitation and delirium

49 Richmond agitation-sedation scale (RASS) and Confusion
50 Assessment Method for ICU patients (CAM-ICU)

51 d) Cognitive function

52 Mini mental state examination (MMSE)

53 e) Renal function

54 Blood urea nitrogen (BUN)

55 creatinine levels

56 estimated glomerular filtration rate

57 daily urinary output

58 requirement for renal replacement therapy

59 f) Inflammatory markers

60 C-reactive protein (CRP)

61 procalcitonin (PCT)

62 g) Organ failure control

63 The Sequential Organ Failure Assessment (SOFA) score

64 h) Coagulopathy control

65 The Disseminated Intravascular Coagulation (DIC) score from
66 the Japanese Association for Acute Medicine (JAAM)

67 i) Nutrition control

68 The daily energy intake by enteral nutrition

69 j) Sedation control

70 The doses of sedative drugs and analgesic drugs

71

72 *Adverse events*

73

74 a) Occurrence of arrhythmia or myocardial ischemia

75

76 **Study Design**

77 The DESIRE trial was a multicenter, open-label, randomized

78 controlled trial with blinded-endpoint assessment. It enrolls patients

79 who were 20 years old or older, had sepsis, and needed mechanical

80 ventilation for at least 24 hours. Patient enrollment started in

81 January 2013 and was completed in January 2016. Patients were

82 enrolled and followed at 8 ICUs throughout Japan. The institutional

83 review board at each participating hospital approved this trial and

84 written informed consent was obtained from each patient.

85 This study was registered at ClinicalTrials.gov with identifier

86 NCT01760967.

87

88

89 **Sample Size Calculation**

90

91 1. In the subgroup analysis of sepsis patients in the MENDS trial

92 by Pandharipande PP et al., dexmedetomidine resulted in an

93 increased 28-day survival rate (84% in the dexmedetomidine

94 group versus 59% in the control group). From this, we have

95 estimated that the 28-day survival rate will be 80% in the

96 dexmedetomidine group and 60% in the control group. We

97 have estimated that, with a sample size of 172 patients, the

98 study will have 80% power to detect a significant difference

99 using the log-rank test. We have estimated that the rate of

100 dropout or withdrawal will be approximately 15%, and thus we

101 plan to enroll 200 patients.

102

103 **Statistical Analyses**

104 Patients were followed until 28 days after initiation of
105 mechanical ventilation. All time-to-event data were censored at 28
106 days. Clinical outcomes were analyzed according to the intention-
107 to-treat principle.

108
109 *Clinical Characteristics*

110 The display of the background

111

112 Factors: The bellow factors.

113 Aim: We can understand clinical characteristics of the
114 patients by classifying and analyzing the
115 background of each group.

116 Expression:

117 Category data: The number of patients and
118 percentage.

119 Continuation data: Mean, SD, median, interquartile
120 range (IQR), the maximum, and the minimum.

121

122 Clinical Characteristics

123 Category data:

124

Sex

125

COPD

126

Soft Tissue Infection

127

Emergency surgery

128

RRT

129

Comorbidities

130

Immunocompromised

131

Chronic hemodialysis

132

Chronic respiratory disorder

133

Chronic heart failure

134

Liver insufficiency

135

Site of infection

136

Abdomen

137

Thorax

138

Urinary tract

139

Pancreatitis

140

Skin and soft tissue

141

CNS

142 Others
143
144 Continuation data:
145 Age
146 Body weight
147 Lactate level
148 CRP
149 PCT
150
151

152 **The main statistical analysis for efficacy**

153

154 Both comparisons should meet the significance to determine the
155 efficacy of treatment group.

156

157 *Comparison between groups of 28-day mortality*

158 **Measure:** Death until 28 days after the initiation of
159 mechanical ventilation. Patients who were alive at 28 days
160 were censored at 28 days.

161 **Aim:** Comparison of the occurrence of the events between
162 groups

163 **Test:** Log-rank test, Cox proportional hazard model

164 **Significance:** Two-sided p values of less than 0.05 were
165 considered statistically significant.

166 **Confidence interval:** 95%confidence interval (CI) of the
167 hazard ratio were calculated.

168 **Expression:** The number of the occurrence of the events,
169 Cumulative incidence, and hazard ratio.

170

171 Using the Cox proportional hazard model, proportional
172 hazard assumptions were assessed on the plots of log (time)
173 vs log [-log(survival)] stratified by index variables. Patients
174 with missing values for any selected variable were excluded
175 from the analyses that used the variable.

176

177 *Comparison between groups of 28-day ventilator free days*

178 **Measure:** 28-days ventilator free days = 28 or days alive –
179 days under mechanical ventilation

180 **Aim:** Comparison of the length between groups

181 **Test:** Wilcoxon rank sum test

182 **Significance:** Two-sided p values of less than 0.05 were
183 considered statistically significant.

184 **Confidence interval:** NA.

185 **Expression:** The median and interquartile range.

186

187

188

189 **The secondary statistical analysis for efficacy**

190

191 28-day mortality

192 **Measure:** Death during 28 days

193 **Aim:** Comparison of the occurrence of the events between
194 groups

195 **Test:** Chi-square test or Fisher exact test

196 **Significance:** Two-sided p values of less than 0.05 were
197 considered statistically significant.

198 **Confidence interval:** NA.

199 **Expression:** The number of the occurrence of the events,
200 the ratio of the occurrence of the events.

201

202 Length of ICU stay

203 **Measure:** Days in ICU

204 **Aim:** Comparison of the length between groups

205 **Test:** Wilcoxon rank sum test

206 **Significance:** Two-sided p values of less than 0.05 were
207 considered statistically significant.

208 **Confidence interval:** NA.

209 **Expression:** The median and interquartile range.

210

211 Length of hospital stay

212 **Measure:** Days in hospital

213 **Aim:** Comparison of the length between groups

214 **Test:** Wilcoxon rank sum test

215 **Significance:** Two-sided p values of less than 0.05 were
216 considered statistically significant.

217 **Confidence interval:** NA.

218 **Expression:** The median and interquartile range.

219

220 Agitation and delirium

221 **Measure 1:** Controlled sedation as an RASS score between
222 -3 and +1

223 **Measure 2:** Delirium and coma free status

224 **Aim:** Comparison of the rate of controlled sedation or
225 delirium and coma free over time between groups

226 **Test:** Chi-square test or Fisher exact test at each day

227 **Significance:** Two-sided p values of less than 0.05 were
228 considered statistically significant.

229 **Confidence interval:** NA.
230 **Expression 1:** The rate of the controlled sedation patients.
231 **Expression 2:** The rate of delirium or coma free patients.

232
233

234 Generalized linear model accounting for repeated
235 measurements was used to examine the effect of
236 dexmedetomidine on the sedation status or free from
237 delirium. GENMOD procedure with logit function was
238 planned and the status of patients was included in the
239 dependent variable and treatment allocation was in the
240 independent variable with repeated variable of patients.

241

242 Cognitive function

243 **Measure:** Mini mental state examination (MMSE)

244 **Aim:** Comparison of MMSE between groups

245 **Test:** Wilcoxon rank sum test

246 **Significance:** Two-sided p values of less than 0.05 were
247 considered statistically significant.

248 **Confidence interval:** NA.

249 **Expression:** The median and interquartile range.

250

251 Renal function

252 **Measure 1:** Blood urea nitrogen (BUN); creatinine levels;
253 estimated glomerular filtration rate; daily urinary output

254 **Measure 2:** requirement for renal replacement therapy

255 **Aim:** Comparison of renal function between groups

256 **Test 1:** Wilcoxon rank sum test

257 **Test 2:** Chi-square test or Fisher exact test

258 **Significance:** Two-sided p values of less than 0.05 were
259 considered statistically significant.

260 **Confidence interval:** NA.

261 **Expression 1:** The median and interquartile range.

262 **Expression 2:** The number of the occurrence of the events,
263 the ratio of the occurrence of the events.

264

265 Inflammatory markers

266 **Measure:** C-reactive protein (CRP), procalcitonin (PCT)

267 **Aim:** Comparison of Inflammatory markers between groups

268 **Test:** Wilcoxon rank sum test

269 **Significance:** Two-sided p values of less than 0.05 were
270 considered statistically significant.

271 **Confidence interval:** NA.

272 **Expression:** The median and interquartile range.

273

274 Organ failure control

275 **Measure:** The Sequential Organ Failure Assessment
276 (SOFA) score

277 **Aim:** Comparison of SOFA score between groups

278 **Test:** Wilcoxon rank sum test

279 **Significance:** Two-sided p values of less than 0.05 were
280 considered statistically significant.

281 **Confidence interval:** NA.

282 **Expression:** The median and interquartile range.

283

284 Coagulopathy control

285 **Measure:** The Disseminated Intravascular Coagulation (DIC)
286 score from the Japanese Association for Acute Medicine
287 (JAAM)

288 **Aim:** Comparison of DIC score between groups

289 **Test:** Wilcoxon rank sum test

290 **Significance:** Two-sided p values of less than 0.05 were
291 considered statistically significant.

292 **Confidence interval:** NA.

293 **Expression:** The median and interquartile range.

294

295 Nutrition control

296 **Measure:** The daily energy intake by enteral nutrition

297 **Aim:** Comparison of daily energy intake between groups

298 **Test:** Wilcoxon rank sum test

299 **Significance:** Two-sided p values of less than 0.05 were
300 considered statistically significant.

301 **Confidence interval:** NA.

302 **Expression:** The median and interquartile range.

303

304 Sedation control

305 **Measure 1:** use of sedative drugs and analgesic drugs

306 **Measure 2:** doses of sedative drugs and analgesic drugs

307 **Aim:** Comparison of renal function between groups

308 **Test 1:** Chi-square test or Fisher exact test

309 **Test 2:** Wilcoxon rank sum test
310 **Significance:** Two-sided p values of less than 0.05 were
311 considered statistically significant.
312 **Confidence interval:** NA.
313 **Expression 1:** The number of the occurrence of the events,
314 the ratio of the occurrence of the events.
315 **Expression 2:** The median and interquartile range.
316
317

318 **Statistical Analysis for Safety**

319

320 Adverse events

321 **Measure:** Occurrence of arrhythmia and cardiac ischemia
322 during 28 days

323 **Aim:** Comparison of the occurrence of the events between
324 groups

325 **Test:** Chi-square test or Fisher exact test

326 **Significance:** Two-sided p values of less than 0.05 were
327 considered statistically significant.

328 **Confidence interval:** NA.

329 **Expression:** The number of the occurrence of the events,
330 the ratio of the occurrence of the events.
331

332 **Sub-group Analyses**

333 **Factors:**

334 Age (>or = 65 year-old, or < 65 year-old)

335 APACHE II (> or = median, or < median)

336 Shock (cardiovascular scale of SOFA score > or = 3, or < 3)

337 Site of Infection (Abdomen, Thorax, or others)

338

339 **Events:** mortality

340 **Measure:** The period to event occurring (censored)

341 **The end of the study:** The end of follow up

342 **Aim:** Comparison of the occurrence of the events between
343 groups

344 **Test:** Log-rank test

345 **Significance:** Two-sided p values of less than 0.05 were
346 considered statistically significant.

347 **Confidence interval:** 95%confidence interval (CI) of the
348 occurrence of the events and hazard ratio were calculated.

349 **Expression:** The number of the occurrence of the events,
350 the ratio of the occurrence of the events, and hazard ratio.

351

352

353

354 **Exploratory Analyses**

355

356 Other exploratory analyses were not decided at the time of
357 writing the SAP but allowed for exploratory purpose.

358 The analyses methods should be justified and clearly
359 described in the manuscript which reports the exploratory
360 analyses.