Effect of an enhanced recovery after surgery protocol in patients undergoing pancreaticoduodenectomy: A randomized controlled trial

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Abstract

Background & Aims: Evidence of the advantages of enhanced recovery after surgery (ERAS) protocols following pancreaticoduodenectomy (PD) is limited. The aim of this study was to examine the efficiency of ERAS protocols in patients following PD.

Methods: Between June 2014 and October 2016, patients undergoing PD were randomly assigned to receive ERAS protocols or standard care. The primary endpoint was the postoperative length of stay. Secondary endpoints included postoperative complications, postoperative quality-of-life (QoR-40J), readmission, and medical cost.

Results: Of 80 eligible patients, 74 were analyzed in intention-to-treat principles: 37 in the control group and 37 in the ERAS group. The mean length of stay in the ERAS group was significantly shorter than that in the control group (20.1 ± 5.4 vs 26.9 ± 13.5 days, $P < 0.001$). The ERAS group had a significantly lower percentage of postoperative complications (32.4% vs 56.8%, $P = 0.034$) and readmissions (0% vs 8.1%, $P = 0.038$). Quality-of-life was also significantly better in the ERAS group (184 ± 12.4 vs 177 ± 14.5, $P = 0.022$). The total medical cost was lower in the ERAS group, but not significantly ($25445 ± 5065 vs $28384 ± 9999, $P = 0.085$).

Conclusions: The optimization of ERAS protocols in patients undergoing PD is safe and accelerates perioperative recovery and quality-of-life, thereby reducing the length of stay. Morbidity was significantly decreased in the ERAS group without compromising surgical outcome.

Registration number UMIN000014068.

Keywords: Enhanced recovery after surgery, Pancreaticoduodenectomy, Goal-directed-therapy, Randomized, Postoperative outcomes

1. Introduction

Despite recent advances in surgical techniques, instruments, and perioperative care, the mortality and morbidity following pancreaticoduodenectomy (PD) remains high, even at high-volume centers in Japan, with a postoperative mortality and overall morbidity rate of 2.8–3.5% and 40%, respectively [1,2]. Furthermore, the length of stay (LOS) after PD is more than 30 days in Japan [1]. There is still a great need for further developments in perioperative care to improve postoperative outcomes, leading to shorter LOS.

Enhanced recovery after surgery (ERAS) programs are multimodal strategies aimed to accelerate postoperative recovery and shorten LOS. Several randomized trials for ERAS protocols were performed in patients undergoing colorectal surgery [3–6], and ERAS protocols have provided high-level evidence on improving postoperative outcomes [7]. The results have shown that ERAS protocols are safe and effective in reducing LOS without increasing morbidity. In addition, there has been a consensus agreement established that ERAS should be a standard practice in colorectal surgery [8].

The ERAS society has also recommended guidelines for perioperative items in PD [9,10]. Furthermore, previous meta-analyses have revealed that ERAS pathways for PD might be safe and help to shorten LOS compared with conventional care [11,12]; however, evidence of the efficiency of ERAS pathways for PD remains limited because a randomized controlled trial (RCT) has not yet been performed. Further research is urgently required to investigate the effect of ERAS protocols on perioperative outcomes in patients undergoing PD.

Therefore, this RCT aimed to examine the effect of ERAS protocols in patients following PD. We hypothesized that implementation of ERAS protocols in PD could accelerate postoperative recovery and reduce LOS without increasing morbidity.

2. Materials and methods

2.1. Trial design

This study was a single center, prospective, randomized trial with two parallel treatment groups receiving either ERAS protocols (ERAS group) or standard care (control group). The Ethics Committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital approved this study, and the study was registered at the University Hospital Medical Information Network (UMIN), registration number UMIN000014068.

All 20-to-80-year-old patients undergoing PD at the Okayama University Hospital in Japan were eligible for enrollment. The exclusion criteria were as follows: failure to obtain consent; severe respiratory dysfunction (arterial PaO2 <70 mmHg), severe cardiac dysfunction (New York Heart Association ≥3), severe hepatic dysfunction (Child Pugh classification C), severe renal dysfunction (hemodialysis), pregnancy, preoperative chemotherapy and/or radiation therapy, acute bacterial infection, severe psychiatric disorder, advanced malignancy, palliative surgery, emergency surgery, and when the investigator was unavailable. Written informed consent was obtained from all patients before enrollment and randomization. The details of the surgical techniques were as described elsewhere [13,14]. Abdominal drains were inserted in all patients and removed according to the drain amylase level if no relevant pancreatic fistula (PF) was detected [15].

2.2. Interventions

ERAS protocols were designed according to reviews of previously published ERAS guidelines (Table 1) [9,10]. The details of the ERAS protocols are also described in Supplementary Material 1. We introduced counseling, mobilization, immunonutrition, and no bowel preparation as preoperative factors. Carbohydrate loading was provided to all patients

115 undergoing surgery. Mobilization was assessed and instructed by the rehabilitation team. Oral
116 supplementation (IMPACT; Nestle Health Science, Japan) for 5 days (750 kcal/day) was used
117 as immunonutrition.

118 Regarding intraoperative factors, fluid restriction was performed according to the goal-
119 directed-therapy (GDT) protocol (Fig. 1). The protocol consisted of standardized crystalloid
120 administration (3 mL/kg/hr) with additional colloid boluses based on hemodynamic
121 monitoring (FloTrac, Edwards Lifesciences, Irvine, CA, USA) [16]. The decompressive
122 nasogastric tube was removed at the end of surgery.

123 Regarding postoperative factors, we introduced the following factors: no nasogastric
124 tube, early oral intake, enteral tube feeding, synbiotics, early removal of urinary catheter and
125 drains, fluid restriction, strict glycemic control, standardized multimodal analgesia, anti-
126 thrombotic prophylaxis, and a telephone call on the day after discharge. Oral intake of liquids
127 started on postoperative day (POD) 1–2 and solids on POD 3–4. Concerning enteral tube
128 feeding, oligomeric formula (PEPTINO; Terumo Corporation, Japan) started on POD 1. The
129 rate was adjusted based on oral intake. Prebiotics (GFO; Otsuka Pharmaceutical Co., Ltd,
130 Japan) and probiotics (MIYA-BM; Miyarinsan Pharmaceutical Co., Ltd, Japan) were used as
131 synbiotics. The urinary catheter was removed on POD 2–3. Glycemic control was controlled
132 by diabetologists. Fractionated low-molecular-weight heparin (CLEXANE; Kaken
133 Pharmaceutical Co., Ltd, Japan) was used for one week. Physiotherapy was performed by the
134 rehabilitation team from POD 1 until discharge. A telephone call to confirm the patient's
135 status was made on the day after discharge.

136

137 *2.3. Standard care*

138 Patients received conventional perioperative care in our unit. We performed some of the
139 ERAS items that had already been introduced before starting the trial. Patients preoperatively

received counseling from the attending surgeon and bowel preparation, but no immunonutrition. Treatment with carbohydrates was given to all patients before surgery.

Concerning anesthesia, standardized crystalloid administration was maintained at 10 mL/kg/hr and additional colloid boluses were given based on conventional management. Other intraoperative factors were the same as in the ERAS protocol (Fig. 1).

Postoperative care was performed according to the surgeon's preference. The decompressive nasogastric tube was removed on POD 1 when the output was less than 300 mL/day. Patients did not routinely receive ERAS items. Patients with poor glycemic control (HbA1c ≥8%) received perioperative strict glycemic control by diabetologists. Postoperative mobilization was performed by the ward nursing staff.

2.4. Primary endpoint and sample size

The primary outcome was postoperative LOS. The sample size was calculated based on the primary outcome, mean LOS. Based on our previous data [14], we conservatively speculated that patients treated according to the ERAS protocol would be discharged seven days sooner than those who were managed with standard care. Thus, 74 patients are required to demonstrate a difference between the two arms with 80% power at an alpha error of 5% (nQuery + nTerim 2.0, Statistical Solutions, Boston MA USA). With estimated exclusion after registration or loss to follow-up of six patients, 80 patients were required (40 patients in each arm).

2.5. Secondary endpoint

2.5.1. Postoperative complications

Mortality and morbidity, including PF, delayed gastric emptying (DGE), bile leakage, hemorrhage, and thrombosis were evaluated. Each postoperative event was evaluated

165 according to the Clavien-Dindo classification [17]. PF and DGE were classified into three
166 categories (grades A, B, and C) according to the International Study Group of Pancreatic
167 Surgery guidelines [18,19]. The infectious complications examined were as follows:
168 incisional surgical site infection, organ/space surgical site infection, cholangitis, pneumonia,
169 enteritis, and bacteremia.
170
171 *2.5.2. Compliance with components of the ERAS protocol*
172 Compliance was based on adherence to each of the 13 items in the ERAS protocols.
173
174 *2.5.3. Quality-of-life and readmission*
175 Quality-of-life and readmission were assessed with the Japanese version of the QoR-40
176 (QoR-40J) [20] before discharge as patient-reported outcomes without interpretation by
177 others. Readmission was examined based on 30-day readmission after discharge.
178
179 *2.5.4. Medical cost*
180 The total medical cost was calculated by adding the cost of the initial admission and
181 subsequent readmissions when patients were readmitted. All medical costs included
182 intraoperative costs (operations and anesthesia), wards and beds, laboratory and radiologic
183 examinations, medications, and other minor expenses according to the hospital medical cost
184 charts. Cost data calculated based on Japanese yen were converted to the United States dollar
185 (US $) using an exchange rate of US $1 = Japanese yen103.4 [21].
186
187 *2.5.5. Anesthesia*
188 Anesthesia was assessed based on intraoperative fluid volume (crystalloid and colloid),
189 urine volume, body temperature, and shivering.

190

191 *2.5.6. Postoperative course*

192 The postoperative course was assessed on the day of initiation of oral intake, passing gas
193 and stool, standing, walking, urinary catheter removal, and drain removal. Chronologic
194 changes in body weight, fluid volume, urine volume, and the drain amylase level on POD 1
195 and 3 were also evaluated.

196

197 *2.5.7. Glycemic control*

198 Glycemic control was examined on preoperative HbA1c (%), postoperative blood sugar
199 level at 1 week, and the serum 1,5-anhydroglucitol level on POD 21.

200

201 *2.5.8. Skeletal muscle mass*

202 The skeletal muscle area at the third lumbar vertebral level was calculated by analyzing
203 computed tomography images on the preoperative day and POD 21 (Synapse Vincent;
204 Fujifilm Medical, Japan) [15, 22]. The total cross-sectional skeletal muscle area (cm^2) was
205 divided by height (m^2) to obtain the skeletal muscle index (SMI, cm^2/m^2).

206

207 *2.5.9. Immune response*

208 Immune response was measured using the level of interleukin-6, helper T cell subset (Th
209 1/2), natural killer cell activity, transforming growth factor β1 (TGF-β1) (SRL, Inc., Japan),
210 and serum albumin during perioperative course.

211

212 *2.6. Randomization and blinding*

213 The data center at the Center for Innovative Clinical Medicine, Okayama University
214 Hospital, conducted the randomization by the minimization method using age (≤70 years vs

215 >70 years), sex (women vs men), disease (pancreatic cancer vs others), dilation of the main
216 pancreatic duct (absence vs presence), and diabetes (absence vs presence) before PD as
217 variables. This study was not blinded, which is consistent with other RCTs concerning ERAS
218 protocols in colorectal surgery [3,5,6].
219
220 *2.7. Discharge criteria*
221 Patients meeting the following criteria were eligible for discharge: ability to perform
222 self-caring, adequate pain control, adequate oral intake, independent mobility, normal range
223 of laboratory values, no postoperative complications, and normal vital sign.
224
225 *2.8. Statistical analysis*
226 The primary analysis (primary endpoint) was performed according to the intention-to-
227 treat principles. Data were presented as means (standard deviation) for continuous variables.
228 Categorical data were presented as numbers (percentages). Differences between groups were
229 assessed using the Student *t* test or the Mann-Whitney U-test for continuous variables and χ^2-
230 test for categorical variables. A *P* value of <0.05 was considered significant. Statistical
231 analysis was performed with JMP 11.2.0 software (SAS Institute, Cary, NC, USA).
232
233 **3. Results**
234 *3.1. Study population*
235 A total of 100 patients were screened and 80 patients randomized from June 1, 2014, to
236 October 11, 2016 (Fig. 2). Of the 80 patients, six were excluded (four for not undergoing PD
237 and two for withdrawal of consent). Data analysis was performed on 37 patients in the ERAS
238 group and 37 patients in the control group.
239 The demographic characteristics of the 74 patients are shown in Table 2. The

240 demographic and clinicopathological factors were not significantly different between the two
241 groups. The mean operative time was 407 minutes (247–570 minutes), and the mean blood
242 loss was 205 mL (10–800 mL). As to pancreatic texture, 48 (64.9%) had a soft pancreas, and
243 40 (54.0%) had a normal main pancreatic duct. No significant differences were observed
244 between the groups with regard to operative factors.
245
246 *3.2. Primary endpoint analysis*
247 The mean LOS was 20.1 ± 5.4 days in the ERAS group and 26.8 ± 13.5 days in the
248 control group ($P < 0.001$, Table 3). The median LOS was 19 days (interquartile range, 15.5–
249 25.0 days) in the ERAS group and 23 days (interquartile range, 21.0–29.5 days) in the control
250 group.
251
252 *3.3. Secondary endpoint analysis*
253 Table 3 also presents the summary results of the secondary outcomes.
254
255 *3.3.1. Postoperative complication*
256 There were no mortalities in the present study. The overall morbidity was significantly
257 decreased in the ERAS group ($P = 0.038$). The complications defined as Clavien grade ≥2
258 were significantly lower in the ERAS group than the control group (32.4% vs 56.8%,
259 respectively, $P = 0.034$). Although the incidence of PF and DGE were not significantly
260 different, the ERAS group had a significantly lower percentage of infectious complications
261 then the control group (18.9% vs 40.5%, respectively, $P = 0.04$).
262
263 *3.3.2. Compliance with components of the ERAS protocol*
264 The results of protocol compliance with the 13 items of the ERAS protocol are shown in

265 Table 4. In the ERAS group, 31 patients (84%) were compliant to all preoperative and
266 intraoperative pathways, and 11 patients (30%) were compliant to all postoperative pathways.
267
268 *3.3.3. Quality-of-life and readmission*
269 Completed QoR-40J questionnaires were returned by all patients. The total scores were
270 significantly higher in the ERAS group than in the control group (184 ± 12.4 vs 177 ± 14.5, P
271 = 0.022) (Fig. 3). The 30-day readmission rate was 0% in the ERAS group and 8.1% in the
272 control group (P = 0.038).
273
274 *3.3.4. Medical cost*
275 Although not significant, the total medical cost in the ERAS group was lower than that
276 in the control group ($25445 ± 5065 vs $28384 ± 9999, P = 0.085). However, the cost other
277 than surgical and anesthetic expense was significantly lower in the ERAS group ($12339 ±
278 3946 vs $15363 ± 7766, P = 0.017).
279
280 *3.3.5. Anesthesia*
281 The ERAS group had significantly lower total fluid volume and urine volume (P <
282 0.001). The ERAS group received significantly lower crystalloid volume, but the colloid
283 volume between groups was not different.
284
285 *3.3.6. Postoperative course*
286 The ERAS group had significantly earlier gastrointestinal function and mobilization.
287 The results of chronologic changes in body weight, fluid volume, urine volume, and the drain
288 amylase level are shown in Supplementary Fig. 1. The median duration of postoperative fluid
289 management was 9 days (interquartile range, 6.5–11 days) in the ERAS group and 12 days

290 (interquartile range, 9–17 days) in the control group ($P = 0.01$).

291

292 *3.3.7. Glycemic control*

293 No differences were observed in preoperative HbA1c, blood sugar level, and 1,5-
294 anhydroglucitol level.

295

296 *3.3.8. Skeletal muscle mass*

297 The SMI was not significantly decreased on POD 21 in the ERAS group ($P = 0.94$) but
298 significantly decreased in the control group (Fig. 4).

299

300 *3.3.9. Immune response*

301 No differences in the level of interleukin-6, Th 1/2 and natural killer cell activity, and
302 TGF-β1 were observed between the groups; however, albumin levels on POD 3 and POD 31
303 were significantly higher in the ERAS group ($P < 0.05$) (see Supplementary Fig. 2).

304

305 **4. Discussion**

306 To our best knowledge, this study is the first RCT to investigate the effect of ERAS
307 protocols in patients following PD. The present study suggests that the implementation of
308 ERAS protocols in PD is as safe as conventional care, with significantly improved
309 postoperative recovery and quality-of-life and shortened LOS. Furthermore, ERAS
310 significantly decreased postoperative morbidity and 30-day readmission. Multimodal
311 optimization was associated with earlier gastrointestinal function and mobilization, which
312 facilitated earlier patient recovery.

313 Previous meta-analyses have shown the effect of ERAS pathways for PD [11,12];
314 however, these studies were based on a limited number of studies and did not include any

315 RCTs. Performing RCTs to investigate multimodal interventions like ERAS protocols is
316 considered difficult, but RCTs are required to provide further evidence on ERAS for PD [23].
317 As hypothesized, the present study demonstrated the safety and efficiency of implementing
318 ERAS in PD and supported previous findings.

319 With respect to primary outcome, we selected LOS, which would be the best indicator to
320 evaluate the effect of multimodal ERAS [3–6,11,12]. The present study demonstrated a
321 significant reduction in LOS. This may be clinically important because improving patient
322 recovery results in lower overall morbidities, thus reducing LOS. Indeed, high morbidity was
323 related to additional treatment and extending LOS. However, multiple factors contribute to
324 the timing of discharge including patient recovery and the healthcare system. In Japan, LOS
325 was longer than in other countries [24]. The reasons were that most hospitals usually provide
326 not only postoperative care, but also subsequent rehabilitation in a single hospitalization,
327 which reflects a longer LOS [1]. In this study, the mean LOS of 74 patients was 23.5 days,
328 shorter than that seen in Japanese high-volume hospitals (>30 days) but much longer than
329 that seen in the US (16.7 days) [25]. However, the 30-day readmission rate in this study was
330 4.1%, which is much lower than that seen in the West (>15%) [26,27].

331 This study also demonstrated the efficiency of ERAS protocols for decreasing
332 postoperative morbidity including infectious complications. A previous RCT on colorectal
333 surgery showed that implementation of ERAS reduced infections [28]. In contrast, no
334 significant reduction was found in PF and DGE. ERAS could have a protective effect only on
335 nonsurgical morbidities [29]. The main surgical morbidities in PD were related to PF and
336 were unlikely to be influenced by ERAS [23]. Moreover, we could not find a significant
337 reduction of DGE, unlike a previous meta-analysis [12]. This result may be influenced by the
338 low sample size of this study.

339 In this study, the protocol compliance was 84% for preoperative and intraoperative

340 pathways and 30% for postoperative pathways in the ERAS group. Among ERAS protocols,
341 the compliance with early oral intake and early drain removal was lower. Concerning oral
342 feeding, in our protocol, oral solids were started on POD 3–4; therefore, our results on
343 postoperative oral feeding that began on POD 4 might be late. However, we decided that
344 patients should be given a normal diet after surgery without restrictions. Concerning drain
345 removal, ERAS after PD was adopted only in low-risk patients according to drain amylase in
346 a previous study [30]; however, in this study, it was implemented in all patients including
347 59% of patients with soft pancreas. Higher rates of soft pancreas may have led to lower
348 compliance with drain removal. Although high-risk patients are more prone to morbidity
349 related to PF, this study suggests that ERAS protocols are acceptable in all patients
350 undergoing PD. Indeed, the level of postoperative drain amylase did not differ between the
351 groups. This might suggest that early oral intake or enteral tube feeding did not increase the
352 risk of PF.

353 Analysis of quality-of-life revealed that the ERAS group had significantly better scores.
354 Few studies have dealt with postoperative recovery measured by patient-reported
355 questionnaires. The advantage of patient-reported outcomes was that they allowed a
356 comprehensive assessment of patient condition across several domains in the recovery
357 process [23]. A previous study showed that ERAS after PD did not influence the quality-of-
358 life [31], while this study showed significant differences in QoR-40J score. Multidisciplinary
359 support by specialized teams could contribute to improving patient quality-of-life compared
360 with the conventional approach.

361 ERAS pathways have been reported to reduce healthcare costs during PD [12]. In this
362 study, the cost, other than surgical and anesthetic costs, was significantly lower in the ERAS
363 group; however, total medical cost was not different. The reasons may be that approximately
364 half of the total costs were surgical and anesthetic cost, and the number of subjects was small.

However, the calculated difference of $2,939 per patient represented the overall cost-effectiveness of ERAS. Shorter LOS and lower overall morbidity may contribute to lower medical costs.

Another topic of concern in anesthesia is the fact that identifying the optimal fluid amount is still controversial despite recommendations of near-zero fluid balance to avoid fluid overload. Recently GDT has been recognized as an important element of ERAS [32]. Furthermore, previous meta-analyses have shown that GDT strategies improved postoperative outcomes [33,34]. However, only a few studies have focused on GDT in patients undergoing PD [35]. In this study, the ERAS group received significantly less intraoperative fluids according to the GDT protocol. Although our GDT protocol consisted of a lower fluid allowance than the previous fluid restriction policy (between 5 and 10 mL/kg/hr) [35,36], we could perform GDT without adding more fluids than allowed by the protocol. Less blood loss and a lower transfusion rate contributed to the safety of the protocol. In particular, 31 (83.8%) patients in the ERAS group received additional colloid boluses compared with 19 (51.4%) in the control group; the colloid volume between groups did not differ. We believe that our GDT protocol is safe and effective, but further studies will be needed to identify more optimal fluid balance.

Concerning postoperative clinical course, the present study showed that implementation of ERAS could contribute to earlier gastrointestinal function and mobilization without compromising patient safety. To keep a near-zero fluid balance, postoperative fluid allowance was kept significantly lower in the ERAS group without increasing adverse events. Furthermore, ERAS prevented postoperative weight reduction. Although postoperative enteral tube feeding may increase blood sugar level, the blood sugar level in the ERAS group was controlled at the same value as the control group with strict glycemic control.

Recent researchers have advocated body composition measurements, such as skeletal

390 muscle mass, to assess sarcopenia. However, there are no studies investigating perioperative
391 changes of muscle mass and the impact of ERAS on muscle mass. The present results
392 indicate that implementation of ERAS could have an effect on preventing skeletal muscle
393 depletion during the perioperative course.

394 There were even fewer studies assessing the association between ERAS and
395 physiological outcomes including immune response markers. Contrary to our expectation, no
396 difference was found in the inflammatory cytokine level. It is likely that PD itself introduces
397 a large amount of physiologic stress, and that the impact of ERAS would not affect the
398 overall stress level. Conversely, ERAS contributed to improved postoperative albumin levels.
399 These results suggest that ERAS could improve a malnourished status quickly. More relevant
400 physiological markers should be investigated.

401 Despite our important findings, several limitations should be acknowledged. First, this
402 was a small-sized, single-center study conducted at a high-volume institution in Japan. The
403 findings may be different for studies conducted in other hospitals or in other countries.
404 Moreover, there has been no multi-center study to investigate ERAS protocols in PD. A
405 multi-center study should be conducted in the future. Second, the study design did not include
406 blinding, which has been used in many ERAS trials [29]. Clearly, blinded implementation of
407 the ERAS was impossible. Therefore, all endpoints and objective criteria were strictly
408 standardized before starting the trial to decrease bias. Only patients meeting the discharge
409 criteria were eligible for discharge in both groups. Furthermore, two surgeons primarily
410 performed perioperative management in the ERAS group and other surgeons primarily
411 performed perioperative management in the control group. We had neutral expectations for
412 both groups before starting the RCT; therefore, the possibility of bias was relatively limited.
413 Third, some ERAS items recommended by the guideline were not included in the control
414 group because they were not included in our previous conventional management. Other

ERAS items were modified in the ERAS group. To compare the differences between conventional management and ERAS management, we continued our conventional management in the control group and introduced ERAS items in ERAS group. Concerning anti-thrombotic prophylaxis, the incidence of pulmonary embolism after PD has been reported to be only 0.2% in Japan [2]; therefore, anti-thrombotic prophylaxis was not routinely included in conventional care at our unit. Although administration for 4 weeks is recommended [9,10], we stopped anti-thrombotic prophylaxis one week after surgery in the ERAS group after confirming there were no signs of thrombosis on postoperative CT images and the patient had independent mobility. Fourth, we excluded 20 patients because of severe organ dysfunction or preoperative chemotherapy. However, a greater proportion of patients with pancreatic cancer may receive preoperative systemic treatment with chemotherapy [37]. Future studies should clarify the effect of ERAS in these high-risk patients. Fifth, it is unclear which factors were most associated with a reduction in LOS. However, it was revealed that the ERAS program itself was the only factor independently associated with shorter LOS [38]. Finally, the long-term outcomes of ERAS remain unclear. Long-term results should be investigated in future studies.

In conclusion, this RCT demonstrated that optimization of ERAS protocols in patients undergoing PD can be safe and effective. Implementation of ERAS in PD contributed to earlier recovery and a shorter hospital stay without compromising surgical outcomes. ERAS protocols could also improve quality-of-life and save on medical costs.

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Statement of Authorship

KT and RY were involved in the development of overall study design, conducted overall study managements and data collection, contributed to writing the manuscript, and were responsible for enrolment and informed consent for general population participants. TY, YU, DN, TK, and TF were involved in the study design, conducted the study, and contributed to writing the manuscript in the field of gastroenterological surgery. SH was involved in the study design, calculated the sample size, and contributed to data analysis and writing the manuscript as a statistician. TM and HM were involved in the study design, conducted the study and data collection and contributed to writing the manuscript in the field of anesthesiology. JE and JW were involved in the study design, conducted the study and data collection and contributed to writing the manuscript in the field of glycemic management. MS was involved in the study design, conducted the study and data collection, and contributed to writing the manuscript in the field of rehabilitation. All authors read and approved the final version of the article.

Conflict of interest statement

The authors declare no conflicts of interest.

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Clinical trial registration

The Ethics Committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital approved this study, and the trial was registered at the University Hospital Medical Information Network (UMIN), registration number UMIN000014068.

Appendix A. Supplementary data

Supplementary data related to this article can be found.

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597 uncomplicated pancreaticoduodenectomy. J Pancreas 2013;14:63–70.

598

599 **Tables**

600 **Table 1**

601 ERAS protocols and conventional care

	ERAS protocol	Standard care
Preoperative factors	Counseling	Advice given by surgeon
	Assessment and guidance of mobilization	
	Immunonutrition	No immunonutrition
	No bowel preparation	Bowel preparation
	Fasting and carbohydrate loading	Fasting and carbohydrate loading
Intraoperative factors	No premedication	No premedication
Maintenance	Total intravenous anesthesia	Total intravenous anesthesia
	Fluid restriction (Goal-directed-therapy)	Conventional fluid management
Avoiding hypothermia	Using forced-air warming	Using forced-air warming
Analgesia	Epidural analgesia	Epidural analgesia
Postoperative factors	No nasogastric tube	Nasogastric tube removal on POD1
	Early oral intake	Care according to surgeon's preference
	Enteral tube feeding	
	Synbiotics	
	Early removal of urinary catheter	
	Early removal of drains at low	

	risk	
	Fluid restriction	
	Strict glycemic control	
	Standardized multimodal analgesia	
	Anti-thrombotic prophylaxis	
	Early scheduled mobilization	Ward mobilization by nurses
After discharge	Telephone call	No telephone call

602 ERAS, Enhanced Recovery After Surgery; POD, postoperative day.

603 **Table 2**

604 Demographic and clinicopathological factors between ERAS and standard care groups

	ERAS group (n = 37)	Control group (n = 37)	*P* value
Demographic variable:			
Sex (males, %)	20 (54)	20 (54)	1.00
Age (years)	67.8 (9.7)	66.8 (9.3)	0.42
BMI (kg/m^2)	22.1 (3.0)	21.7 (2.8)	0.61
ASA physical status:			
Grades 1/2/3	3/23/11	6/26/5	0.17
Comorbidity:			
Hypertension	18 (49)	14 (38)	0.35
Diabetes	14 (38)	15 (41)	0.81
Etiology of disease:			
Pancreatic adenocarcinoma	13 (35)	11 (30)	0.84
Bile duct carcinoma	5 (14)	7 (19)	
Ampullary adenocarcinoma	5 (14)	7 (19)	
Duodenal adenocarcinoma	3 (8)	1 (3)	
IPMN	6 (16)	5 (14)	
Other disease	5 (14)	6 (16)	
Preoperative biliary drainage	10 (27)	14 (38)	0.32
Operative factors:			
PPPD/SSPPD/PD	6/28/3	8/27/2	0.78
Vascular reconstruction	11 (30)	7 (19)	0.28
Operative time (min)	407 (82)	407 (75)	0.91

Blood loss (mL)	194 (180)	216 (158)	0.38
Transfusion	2 (5.4)	2 (5.4)	1.00
Pancreatic texture:			
Soft/Hard	22/15	26/11	0.33
MPD diameter:			
Normal (≤3 mm)/Dilated (>3 mm)	19/18	21/16	0.64

Data are presented as numbers (percentages) or means (standard deviation).

ASA, American Society of Anesthesiologists; BMI, body mass index; ERAS, Enhanced Recovery After Surgery; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy.

610 **Table 3**

611 Primary and secondary outcomes

	ERAS group (n = 37)	Control group (n = 37)	*P* value
Length of stay (days)	20.1 (5.4)	26.9 (13.5)	<0.001
Complication:			
Mortality	0 (0)	0 (0)	-
Overall morbidity [a] (Grades 0/I/II/III/IV)	14/11/6/6/0	5/11/15/6/0	0.038
PF (0/A/B/C)	21/9/6/1	11/16/9/1	0.12
DGE (0/A/B/C)	32/1/4/0	30/4/3/0	0.34
Bile leakage	1 (3)	3 (8)	0.29
Hemorrhage	1 (3)	1 (3)	1.00
Thrombosis	1 (3)	2 (5)	0.55
Any Infections	7 (19)	15 (41)	0.04
Incisional SSI	5 (14)	9 (24)	0.23
Organ/space SSI	1 (3)	4 (11)	0.15
Cholangitis	1 (3)	1 (3)	1.00
Pneumonia	1 (3)	0 (0)	0.24
Enteritis	0 (0)	0 (0)	-
Bacteremia	1 (3)	4 (11)	0.15
Others	0 (0)	0 (0)	-
Quality-of-life (QoR-40J)	184 (12.4)	177 (14.5)	0.022
Readmission	0 (0)	3 (8)	0.038
Total Cost ($)	25,445 (5,065)	28,384 (9,999)	0.085

Surgery/Anesthesia ($)	13,107 (2,199)	13,021 (2,940)	0.66
Others [b] ($)	12,339 (3,946)	15,363 (7,766)	0.017
Anesthesia:			
Total fluid volume (mL)	2,139 (872)	4,569 (995)	<0.001
Crystalloid volume (mL)	1,657 (765)	4,186 (983)	<0.001
Colloid volume (mL)	482 (342)	364 (421)	0.054
Urine volume (mL)	421 (341)	841 (387)	<0.001
Temperature (Max, degrees)	36.2 (0.5)	35.9 (0.6)	0.012
Temperature (Min, degrees)	37.2 (0.5)	36.9 (0.5)	0.008
Shivering	7 (19)	16 (43)	0.022
Postoperative course:			
Gastrointestinal function			
First liquid (days)	2.0 (1.5)	3.9 (2.0)	<0.001
First solid (days)	4.1 (2.1)	5.8 (2.7)	<0.001
First bowel gas (days)	1.6 (0.7)	3.1 (1.5)	<0.001
First stool (days)	2.5 (1.2)	5.1 (2.3)	<0.001
Mobilization			
Standing position (days)	1.4 (0.6)	2.1 (0.7)	<0.001
Walking (days)	1.9 (0.7)	2.6 (1.1)	0.005
Urinary catheter removal (days)	2.9 (0.4)	6.2 (2.1)	<0.001
Drain removal (days)	12.4 (8.4)	18.1 (15.3)	0.057
Glycemic control:			
Preoperative HbA1c (%)	6.1 (0.9)	6.5 (1.4)	0.33
Blood sugar level (POD 1-7, mg/dL)	156 (27.9)	145 (27.8)	0.11
1,5-anhydroglucitol (POD 21, μg/mL)	11.0 (5.6)	9.3 (5.6)	0.16

612 Data are presented as numbers (percentages) or means (standard deviation).

613 [a] Stratified according Clavien-Dindo classification.

614 [b] Calculated medical costs for wards and beds, laboratory and radiologic examinations,

615 medications, and other minor expenses.

616 DGE, delayed gastric emptying; ERAS, Enhanced Recovery After Surgery; PF, pancreatic

617 fistula; POD, postoperative day; SSI, surgical site infection.

618

Table 4

Protocol compliance

	ERAS group (n = 37)	Control group (n = 37)	*P* value
Preoperative compliance:			
Counseling	37 (100)	0 (0)	<0.001
Mobilization	37 (100)	0 (0)	<0.001
No bowel preparation	36 (97)	0 (0)	<0.001
Oral carbohydrate loading	37 (100)	37 (100)	-
Intraoperative compliance:			
No premedication	37 (100)	37 (100)	-
Goal-directed-therapy	36 (97)	0 (0)	<0.001
Avoiding hypothermia	37 (100)	37 (100)	-
Epidural analgesia	33 (89)	34 (92)	0.69
Postoperative compliance:			
No nasogastric tube	37 (100)	12 (32)	<0.001
Early oral intake [a]	16 (43)	2 (5)	<0.001
Early removal of urinary catheter [b]	36 (97)	1 (3)	<0.001
Early removal of drains [c]	19 (51)	7 (19)	0.003
Early scheduled mobilization	37 (100)	1 (3)	<0.001

Data are presented as numbers (percentages).

[a] Starting oral intake of solids within the first 3 postoperative days.

[b] Within postoperative day 3.

[c] Within postoperative day 7.

ERAS, Enhanced Recovery After Surgery.

626 **Figure legends**

627

628 **Fig. 1.** Anesthesia protocol (A) and goal-directed-therapy (GDT) protocol (B). Concerning
629 GDT protocol, the hemodynamic monitoring was based on the stroke volume index (SVI);
630 additional colloid bolus was given when SVI was less than 30 or monitoring when SVI was
631 more than 30. The mean arterial pressure (mAP) was kept more than 55 mmHg at least using
632 inotropic agents guided by cardiac index (CI). ERAS, enhanced recovery after surgery.

633

634 **Fig. 2.** CONSORT flow diagram for the trial.

635

636 **Fig. 3.** Quality-of-life before discharge in the two groups, assessed using the Japanese version
637 of the QoR-40 (QoR-40J) (100 is the best outcome).

638

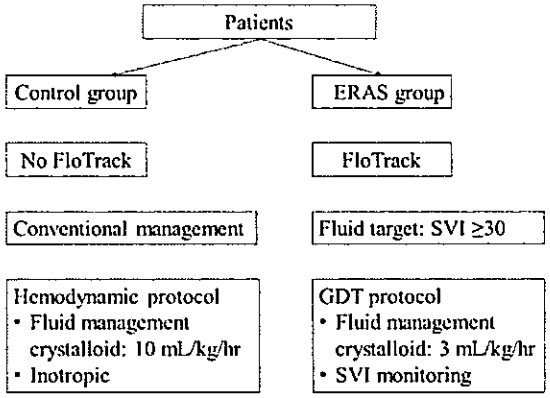
639 **Fig. 4.** Skeletal muscle index (cm^2/m^2) in the two groups during the first 21 days after PD.
640 Boxes show median with interquartile range; whiskers give the range.

641

642 **Figures**

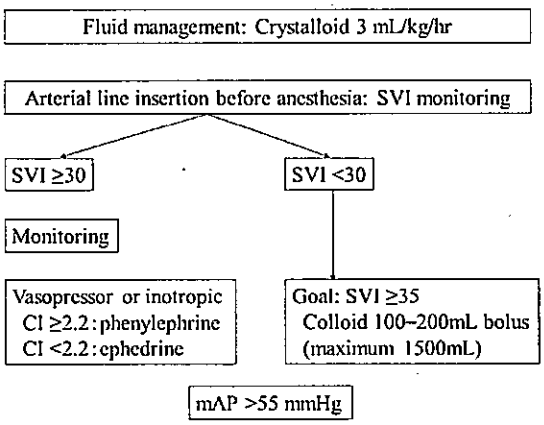
643

644 A. Anesthesia protocol



645

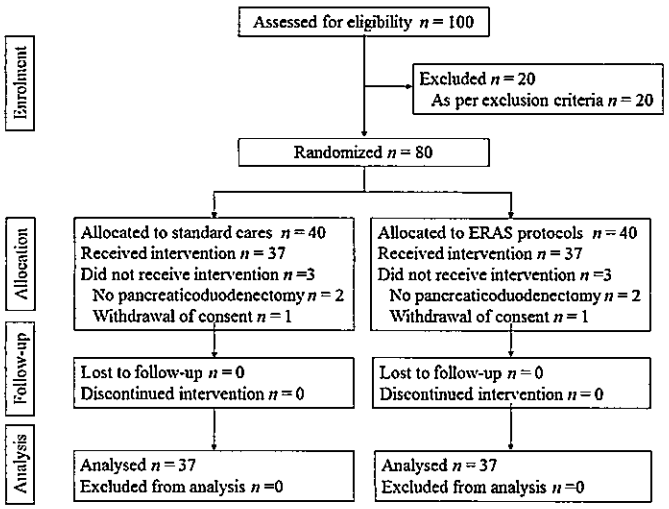
646 B. Goal-directed-therapy protocol



647

648 **Fig. 1.**

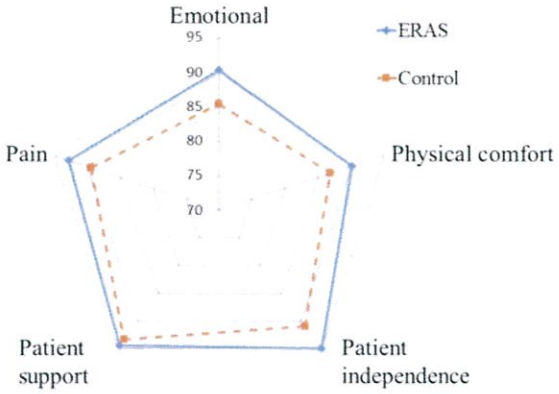
649



650

651 **Fig. 2.**

652



653

654 **Fig. 3.**

655

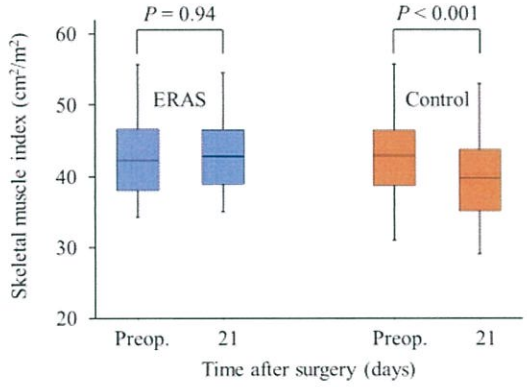

P = 0.94
P < 0.001
ERAS
Control
Skeletal muscle index (cm²/m²)
60
50
40
30
20
Preop.
21
Preop.
21
Time after surgery (days)

Fig. 4.