

A hospital-to-home evaluation of an enhanced recovery protocol for elective pancreaticoduodenectomy in China

A cohort study

Wei Su, MD^{a,b}, Fangyan Lu, BSN^a, Xiaoyu Zhang, MBBS^{a,b}, Guogang Li, MD^{a,b}, Wei Chen, PhD^{a,b}, Tao Ma, PhD^{a,b}, Shunliang Gao, MS^{a,b}, Jianying Lou, MD^{a,b}, Xueli Bai, MD, PhD^{a,b,*}, Tingbo Liang, MD, PhD^{a,b,c,*}

Abstract

Enhanced recovery after surgery (ERAS) programs have been shown to decrease postoperative complications and hospital stay in pancreaticoduodenectomy. However, no studies concerned recovery after discharge except readmission. This study evaluated an ERAS program for pancreaticoduodenectomy from hospital to home.

A prospective ERAS cohort undergoing elective pancreaticoduodenectomy was compared with a retrospective control group in terms of postoperative complications and hospital stay, and home recovery after discharge. Propensity-score matching was used to balance their baselines.

Two groups of 31 patients with similar propensity scores were established. Postoperative morbidities were 18 of 31 and 26 of 31 in the ERAS and control groups, respectively ($P=.06$). Patients in the ERAS group suffered from fewer cardiovascular complications (3/31 vs 11/31; $P=.04$) and intestinal dysbacteriosis (4/31 vs 13/31; $P=.04$). Median postoperative hospital stay was shorter in the ERAS group (8 vs 16 days; $P<.001$). Although the 2 groups were similar in terms of sleep, defecation, vigor, performance status, and pain control in first month after discharge, patients in the ERAS group enjoyed better food intake recovery (18/31 vs 5/31 in first week, $P=.002$; 22/31 vs 9/31 in second week, $P=.008$; 23/31 vs 13/31 in fourth week, $P=.01$) and fewer weight loss (10/31 vs 19/31; $P=.05$). Multivariate analyses showed that both improvements were associated with no bowel preparation.

ERAS implementation in selected patients undergoing pancreaticoduodenectomy could promise better outcomes, not only in the hospital but also at home in the short term.

Abbreviations: 5-HT = 5-hydroxytryptamine, ASA = American Society of Anesthesiologists score, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, ERAS = enhanced recovery after surgery, ICU = intensive care unit, IPC = intermittent pneumatic compression, IQR = interquartile range, LMWH = low molecular weight heparin, LOPH = length of postoperative hospital stay, NGT = nasogastric tube, NRS = numerical rating scale, NSAIDs = nonsteroidal anti-inflammatory drugs, OR = odd risk, PD = pancreaticoduodenectomy, POD = postoperative day, PONV = postoperative nausea and vomiting, WHO = World Health Organization.

Keywords: after-hospital assessment, enhanced recovery after surgery, fast track, pancreaticoduodenectomy, propensity-score matching

Editor: Kelvin Ng.

Funding: This study was funded by the National High Technology Research and Development Program of China (SS2015AA020405), the Training Program of Key Program of National Natural Science Foundation of China (91442115), the Key Innovative Team for the Diagnosis and Treatment of Pancreatic Cancer of Zhejiang Province (2013TD06), the Key Program of National Natural Science Foundation of China (81530079), and the Key Research and Development Project of Zhejiang Province (2015C03G2010148).

The authors declared no conflict of interest.

Supplemental Digital Content is available for this article.

^a Department of Hepatobiliary and Pancreatic Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine, ^b Key Laboratory of Pancreatic Disease of Zhejiang Province, Hangzhou, ^c Zhejiang University, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China.

* Correspondence: Tingbo Liang and Xueli Bai, No. 88 Jiefang Road, Hangzhou 310009, China (e-mails: liangtingbo@zju.edu.cn, shirleybai@zju.edu.cn).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2017) 96:41(e8206)

Received: 10 June 2017 / Received in final form: 8 September 2017 / Accepted: 11 September 2017

<http://dx.doi.org/10.1097/MD.00000000000008206>

1. Introduction

Enhanced Recovery After Surgery (ERAS) program, also referred to as Fast-Track pathway, is an optimized framework of perioperative care that aims to improve safety and clinical outcomes.^[1] It is a multimodal approach that involves close collaboration among surgeons, anesthesiologists, nurses, and other paramedics. Since it was initiated by Kehlet^[2] in the 1990s for colonic surgery, ERAS programs have been adopted gradually by many other fields of surgery, including major gastrointestinal and liver surgery.^[3,4] By reducing surgical stress, controlling postoperative pain, and promoting early oral diet and mobilization, ERAS programs can shorten the length of postoperative hospital stay (LOPH) and save medical costs without increasing postoperative morbidity, mortality, and readmission rate.^[5]

Pancreaticoduodenectomy (PD) is currently the only curative treatment for periampullary malignancy and pancreatic cancer. However, it is also a high-risk abdominal surgery. In China, the LOPH remains about 20 days, even in high-volume centers.^[6,7] Thus, there may be an opportunity to reduce LOPH by the introduction of ERAS.

Several studies have explored the feasibility and efficacy of ERAS in PD.^[8,9] Evidence indicated that ERAS protocols implemented in PD shortened the LOPH without compromising postoperative outcomes. However, no studies provide data concerning the recovery after discharge, except for readmission. As we all know, the LOPH can still be sensitively influenced by many subjective factors, especially the acceptance or incentives for early discharge. Moreover, earlier discharge may lead to failure to document some delayed complications. Therefore, whether patients in the ERAS group are ready to go home physically and whether they will continue to recover as well as

might in hospital are unknown. This is particularly important in China, where most patients go home after discharge and cannot get professional care. Thus, it would be useful to evaluate the recovery of these patients after discharge.

In the current study, we compared a consecutive cohort of patients undergoing elective PDs before and after implementation of ERAS with regard to postoperative outcomes in hospital and recovery at home. This is the first study evaluating in detail the impact of an enhanced recovery protocol for PD on after-hospital recovery. Our findings will help comprehensively assess the safety and efficacy of ERAS in PD.

2. Material and methods

An ERAS protocol for PD with active contribution from the ERAS Society^[5] was implemented in the Department of Hepatobiliary and Pancreatic Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine, in May 2014 (Table 1). The department is a drafter of ERAS guidelines for hepatobiliary and pancreatic surgery in China.

2.1. Study overview

A registered randomized clinical trial on PD was conducted in this center in 2012.^[10] Correspondingly, an electronic database was developed for prospective data collection, including demographic information and perioperative data since then. To better evaluate postoperative outcomes, follow-ups were done systematically from June 2013 and were entered prospectively into the database.

In the present study, patients undergoing elective PDs were included consecutively from June 2013 to November 2015. Those who stayed in the intensive care unit for more than 24

Table 1

Perioperative care before and after introduction of the enhanced recovery after surgery protocol.

	Pre-ERAS era	ERAS protocol
Day of admission	Conventional informed consent, including the discharge criteria, follow-up plan, and approach of readmission	Conventional informed consent ERAS-specific counseling, including the aim and procedure of ERAS program
Day before surgery	Overnight fasting Oral bowel preparation	Intake of solid food up to 6 h before anesthesia Intake of clear fluids up to 2 h before anesthesia No bowel preparation
Day of surgery	Goal-directed intravenous fluids* Antimicrobial prophylaxis Acid suppression Epidural analgesia Weak-intense intravenous analgesia	Goal-directed intravenous fluids* Antimicrobial prophylaxis Acid suppression PONV prophylaxis with 5-HT receptor antagonist Epidural analgesia Scheduled intravenous analgesia with NSAIDs and weak opioids
POD 1	Parenteral nutrition Anti-thrombotic prophylaxis with IPC and LMWH Metoclopramide if nausea or vomiting occurred On-bed movement	Parenteral nutrition Anti-thrombotic prophylaxis with IPC and LMWH On-bed movement
POD 2	Removal of urinary catheter after intermittent clipping	Early removal of urinary catheter (within 36 h) Early removal of NGT Bedside sitting and standing for 1 h in total
POD 3	Removal of NGT Oral nutrition depending on patient's progress, such as flatus	Early oral liquids Oral analgesia of NSAIDs if NRS > 3 Assisted walking
POD 4	Untargeted mobilization Oral analgesia if patient demand	Early oral solid food Gradual transfer to regular diet

5-HT = 5-hydroxytryptamine, ERAS = enhanced recovery after surgery, IPC = intermittent pneumatic compression, LMWH = low molecular weight heparin, NGT = nasogastric tube, NRS = numerical rating scale, NSAIDs = non-steroidal anti-inflammatory drugs, POD = postoperative day, PONV = postoperative nausea and vomiting.

*Based on the changes of blood pressure, heart rate, central venous pressure, and central venous oxygen saturation.

Adapted from reference^[5].

Table 2
Baseline characteristics before and after propensity-score matching*.

Characteristics	Before matching			After matching		Standardized differences
	Pre-ERAS (N=40)	ERAS (N=82)	P	Pre-ERAS (N=31)	ERAS (N=31)	
Gender (Male/Female)	26/14	42/40	.15	18/13	19/12	6.6%
Age, y	62 ± 11	61 ± 12	.78	61 ± 11	62 ± 9	9.0%
Body mass index, kg/m ²	23.2 ± 3.4	22.1 ± 2.7	.06	22.7 ± 2.8	22.4 ± 3.0	9.7%
Active smoker	21	28	.05	14	14	0.0%
Comorbid disease						
Cardiovascular disease [†]	20	24	.03	12	12	0.0%
Respiratory disease [‡]	4	10	>.99	3	3	0.0%
Diabetes mellitus	8	16	.95	7	6	8.0%
Serum albumin, g/L	37.8 ± 5.6	37.4 ± 5.5	.70	38.3 ± 5.7	38.1 ± 5.0	3.7%
ASA grade >2	7	17	.67	5	5	0.0%
Malignancy [§]	34	61	.19	26	27	9.2%
Neoadjuvant therapy	0	3	.55	0	0	0.0%
Operation duration, min	379 ± 119	389 ± 121	.68	386 ± 120	388 ± 117	2.2%
Intraoperative blood loss, mL	300 (200, 400)	300 (150, 400)	.68	300 (200, 400)	300 (200, 500)	5.6%
Vascular resection	13	22	.52	9	8	7.2%
Postoperative ICU stay	9	20	.82	7	8	7.5%

ASA=American Society of Anesthesiologists score, ERAS=enhanced recovery after surgery, ICU=intensive care unit, IQR=interquartile range.

*Plus-minus values are means ± standard deviations. A standardized difference of less than 10.0% indicates a relatively small imbalance.

[†]Includes hypertension, coronary heart disease, atrial fibrillation, and cardiomyopathy.

[‡]Includes chronic obstructive pulmonary disease, asthma, obsolete pulmonary tuberculosis, and mild pneumonia.

[§]Originates from pancreas, duodenum, and bile duct.

^{||}The value is median (IQR).

hours were unable to adhere to the protocol and were excluded. A prospective ERAS cohort (May 2014–November 2015) was compared with a retrospective control group (pre-ERAS, June 2013–April 2014) with regard to postoperative recovery, both in hospital and at home. The demographic information, perioperative data, and follow-ups were extracted from the database described above. The compliance with the ERAS protocol was recorded prospectively and was audited monthly by the chief resident in the ERAS group. But it was collected retrospectively in the pre-ERAS group. During the study period, key medical personnel, including surgeons and nurses, stayed the same. Given the imbalance in the baseline characteristics between the 2 groups (Table 2), propensity-score matching was used.

The study received approval from the Medical Ethics Committee of the Second Affiliation Hospital of Zhejiang University School of Medicine.

2.2. Postoperative outcomes

Postoperative complications were documented and graded according to the Dindo–Clavien classification.^[11] Pancreatic fistula, delayed gastric emptying (DGE), postpancreatectomy hemorrhage, biliary leakage, intra-abdominal infection, and pulmonary infection were defined in line with our previous study.^[10] Impaired wound healing was diagnosed according to the definition by Kuppahally et al.^[12] Intestinal dysbacteriosis was diagnosed on the basis of fecal culture of disturbed gut flora, where pathogenic bacteria such as *Staphylococcus aureus* and *Candida albicans* overgrew. Acute heart failure was diagnosed on the basis of an elevated level of serum amino-terminal pro-brain natriuretic peptide (<50 years, >450 pg/mL; 50–75 years, >900 pg/mL; >75 years, >1800 pg/mL).^[13] Arrhythmia was diagnosed on the basis of electrocardiograph changes confirmed by a cardiologist. Pleural effusion was considered as a complication when it was detected by ultrasound or computed

tomography scan, and was severe enough to cause clinical symptoms and require special treatments, such as thoracentesis. Infections of the central venous catheter and the urinary tract were diagnosed on the basis of clinical signs and positive culture results for bacteria.^[14]

2.3. Discharge criteria

Patients were not allowed to leave hospital until they met the following criteria: good function of vital organs; no signs of infection; good pain control, with or without oral analgesics alone; tolerance for solid food; passage of stools; good movement with assistance; and good wound healing.

2.4. Follow-ups

Patients were followed up for at least 4 weeks and were surveyed by telephone on Day 7, Day 14, and Day 28 after discharge. At each time point, patients were asked about their food intake, sleep, defecation, vigor, performance status, pain control and weight changes, using a specially designed form. Food intake was staged into 3 grades according to its change before and after surgery. Patients with Grade A had similar daily food intake to that before surgery. Patients with Grade B had significantly reduced daily food intake, yet ate more than 50% of that before surgery. For those with Grade C, their daily food intake decreased to less than 50% of that before surgery. A patient was considered to have good recovery of food intake if he/she received more than one A scores in the 3 surveys. We documented patients' complaints about sleep at the first 2 surveys and assessed their sleep qualities using Athens Insomnia Scale^[15] at the third survey. A patient was considered to have satisfactory sleep if no complaints about sleep were reported at the first 2 surveys or if the score ranged from 0 to 3 at the third survey. Vigor was assessed using the Surgical Recovery Scale,^[16] and fatigue was

diagnosed if the score < 60. Performance status was scored as 0 to 5 using the Zubrod–Eastern Cooperative Oncology Group–World Health Organization (Zubrod–ECOG–WHO) scale.^[17] Pain was assessed on the basis of a numerical rating scale.^[18] A patient was considered having weight loss if his/her weight was reduced 1 kg or more than that at discharge. In addition, unplanned readmissions and death within 30 days after discharge were recorded. The follow-up was carried out thoroughly by the nursing team.

2.5. Statistical analysis

The propensity score was estimated using a nonparsimonious multivariable logistic-regression model with ERAS or pre-ERAS as the dependent variable and all the baseline characteristics outlined in Table 2 as covariates. Matching was performed using a 1:1 matching protocol without replacement (local algorithm), with a caliper width equal to 20% of the standard deviation of the logit of the propensity score. A standardized difference of less than 10.0% for a given covariate indicated a relatively small imbalance.^[19] In the matched cohort, paired comparisons were performed using McNemar test for binary variables, Wilcoxon signed ranks test for ranked data, and a paired Student *t* test or Wilcoxon paired-sample test for continuous variables. For unpaired data, binary variables were compared using a Chi-square test or Fisher exact test, and continuous variables were compared using Student *t* test or Mann–Whitney *U* test. All possible variables were included for univariate analysis, and variables with *P* values < .1 were considered as candidates for multivariate analysis. To relieve the problem of multicollinearity, variables with a correlation coefficient > 0.8 were included exclusively. Multivariate analysis was performed using binary logistic regression. The selection of stepwise methods depended on C statistics and Hosmer–Lemeshow test. All statistical analyses were conducted using SPSS v23.0 (IBM Corp., Armonk, New York). All reported *P* values were 2-sided and a statistical significance was considered when *P* was no more than .05.

3. Results

A total of 122 eligible patients undergoing elective PDs were identified, of whom 40 were included in the pre-ERAS group and 82 were included in the ERAS group (Table 2). No patients underwent pylori-preserving PD. Before matching, the 2 groups were imbalanced in terms of body mass index, active smoking, and comorbid cardiovascular disease. After propensity-score matching, 2 groups containing 31 patients in each were established. The standardized differences were less than 10.0% for all variables. All the subsequent analyses were based on the matched groups unless indicated otherwise.

3.1. Protocol compliance

The degree of adherence to core protocol elements was summarized in Table 3. In general, mean compliance with these factors was significantly improved after ERAS implementation (43.8% vs 81.2%; *P* = .002).

3.2. Postoperative outcomes in hospital

Compared with those in the pre-ERAS group, patients in the ERAS group tended to suffer from fewer (26/31 vs 18/31; *P* = .06) and minor (*P* = .06) complications (Table 4). The overall

Table 3

Compliance with core ERAS protocol elements.

Elements	Pre-ERAS (N = 31)	ERAS (N = 31)	<i>P</i>
ERAS-specific counseling	0	31	<.001
No bowel preparation	1	29	<.001
Antimicrobial prophylaxis	31	31	—
Goal-directed intravenous fluids	31	31	—
Multimodal analgesia postoperation			
Epidural analgesia	31	31	—
Scheduled intravenous analgesia	23	30	.04
Oral analgesia	6	12	.11
PONV prophylaxis	2	22	<.001
Anti-thrombotic prophylaxis			
IPC	31	31	—
LMWH	24	23	>.99
Early removal of urinary catheter	6	18	.004
Early removal of NGT	5	26	<.001
Early oral diet			
Oral liquids	5	25	<.001
Oral solids	3	20	<.001
Targeted mobilization			
POD1 On-bed movement	24	30	.03
POD2 Off-bed standing	3	19	<.001
POD3 Assisted walking	5	19	.001

ERAS = enhanced recovery after surgery, IPC = intermittent pneumatic compression, LMWH = low molecular weight heparin, NGT = nasogastric tube, POD = postoperative day, PONV = postoperative nausea and vomiting.

Table 4

Postoperative outcomes in hospital.

Outcomes	Pre-ERAS (N = 31)	ERAS (N = 31)	<i>P</i>
Cardiovascular complications*	11	3	.04
Respiratory complications†	6	3	.51
Pancreatic fistula	10	12	.80
Grade A	2	5	
Grade B	7	6	.93‡
Grade C	1	1	
Delayed gastric emptying	7	2	.18
Hemorrhage	4	4	>.99
Biliary leakage	2	1	>.99
Intra-abdominal infection	3	6	.45
Impaired wound healing	0	2	.50
Intestinal dysbacteriosis	13	4	.04
Others‡	4	0	.13
Complications	26	18	.06
Grade I	4	6	
Grade II	16	10	.06¶
Grade III	3	2	
Grade IV	1	0	
Unplanned reoperation	0	1	>.99
LOPH, d	16	8	<.001

ERAS = enhanced recovery after surgery, IQR = interquartile range.

* Includes acute heart failure, emerging arrhythmia, and uncontrollable hypertension.

† Includes emerging or worsened pulmonary infection and pleural effusion.

‡ Compare the severity of complication(s) with treating the uncomplicated as the lowest level.

§ Includes a case of infection of central venous catheterization, a case of urinary tract infection, a case of bowel obstruction, and a case of liver failure.

¶ .06 is the significance for the comparison of grade of complications, which is a ranked variable.

|| The value is median (IQR).

ERAS = enhanced recovery after surgery, IQR = interquartile range.

incidence of cardiovascular complications, including acute heart failure (6/31 vs 3/31; $P = .51$), arrhythmia (4/31 vs 1/31; $P = .38$), and uncontrollable hypertension (1/31 vs 0/31; $P > .99$), was significantly lower in the ERAS group (11/31 vs 3/31; $P = .04$). It should be noted that all the acute heart failure cases were mild, even asymptomatic. Besides, the incidence of intestinal dysbacteriosis was also significantly lower in the ERAS group (13/31 vs 4/31; $P = .04$).

Two patients in the pre-ERAS group and one in the ERAS group underwent endoscopic intervention because of DGE. A patient in the pre-ERAS group underwent thoracentesis because of massive pleural effusion. A patient in the ERAS group underwent unplanned reoperation because of a severe pancreatic fistula. Liver failure occurred in 1 patient in the pre-ERAS group (Grade IV).

Median (interquartile range, IQR) LOPH was largely shortened from 16 (12–24) days to 8 (7–17) days after the implementation of the ERAS program ($P < .001$).

3.3. Home recovery

All patients went home after discharge and no patients were lost to follow-up within 30 days after discharge. During this period, no patients died. However, 2 patients in the ERAS group were readmitted ($P = .50$): 1 on second day after discharge because of severe infection, and the other in second week because of severe abdominal pain.

Generally, most patients achieved acceptable home recovery in the first month after discharge (Fig. 1). Notably, the proportion of patients with Grade A in food intake kept higher in the ERAS group (5/31 vs 18/31 in first week, $P = .002$; 9/31 vs 22/31 in second week, $P = .008$; 13/31 vs 23/31 in fourth week, $P = .01$). Furthermore, weight changes were evaluated at the last survey. Three data in the pre-ERAS group and two data in the ERAS group were unavailable. However, both intention-to-treat analysis with the worst-case scenario (19/31 vs 10/31; $P = .05$) and per-protocol analysis (18/26 vs 7/26; $P = .007$) showed that

the proportion of patients suffering weight loss was lower in the ERAS group.

3.4. Factors influencing postoperative recovery

To explore the factors influencing postoperative recovery, all the baseline variables and core protocol elements were considered. The univariate analyses for cardiovascular complications and intestinal dysbacteriosis were summarized in Tables S1 and S2 (See Supplementary Material, <http://links.lww.com/MD/B893>). And, multivariate regression analyses were performed for good recovery of food intake after discharge and weight loss (Tables 5 and 6). No bowel preparation was suggested as an independent protective factor for both food intake recovery [odds risk (OR) = 4.43; 95% confidence interval (CI): 1.41–13.97; $P = .01$] and weight loss (OR = 0.19; 95% CI: 0.06–0.64; $P = .007$).

4. Discussion

In this before–after cohort of patients undergoing elective PDs, we observed a reduced incidence of postoperative complications, especially cardiovascular complications and intestinal dysbacteriosis, and a shortened LOPH in hospital; an improved recovery of food intake and a decreased rate of weight loss postdischarge after implementation of an ERAS protocol. No bowel preparation was associated with better recovery of food intake and prevention of weight loss. Short-term outcomes, both in hospital and at home, suggested that the ERAS protocol could promise a better and faster recovery after surgery. As far as we know, this is the first study to evaluate comprehensively the impact of an ERAS protocol on patients undergoing elective PDs from hospital to home.

Postoperative outcomes in hospital were documented in detail. The overall morbidity tended to be reduced, in keeping with previous studies.^[20,21] Particularly, cardiovascular complications were found significantly reduced after implementing ERAS, which had been hardly ever reported in previous studies on ERAS

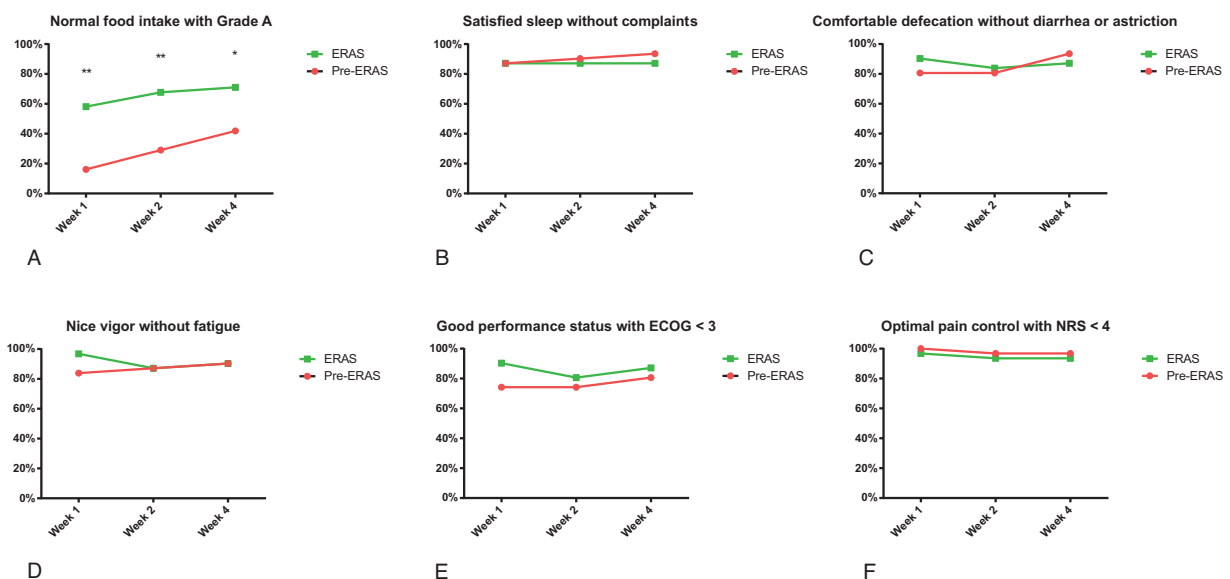


Figure 1. Home recovery in the first 4 weeks after discharge. Patients readmitted were treated as the worst cases in the analysis. ECOG = Eastern Cooperative Oncology Group score, ERAS = enhanced recovery after surgery, NRS = numerical rating scale. Compared with the pre-ERAS group: * $P < .05$; † $P < .01$.

Table 5**Uni- and multivariate analyses for good recovery of food intake after discharge***

Valuables	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Body mass index $\geq 24\text{kg/m}^2$	3.13 (0.93–10.48)	.07	4.56 (1.20–17.39)	.03
No bowel preparation	3.30 (1.16–9.34)	.03	4.43 (1.41–13.97)	.01
PONV prophylaxis	2.56 (0.89–7.32)	.08		
Early removal of NGT	3.82 (1.33–10.94)	.01		
Early oral liquids	3.30 (1.16–9.34)	.03		

CI = confidence interval, NGT = nasogastric tube, OR = odd risk, PONV = postoperative nausea and vomiting.

* All the baseline variables and core protocol elements are considered, and only those with $P < .1$ are listed. Step methods, backward LR; C statistics, .71; P value for Hosmer–Lemeshow test, .97.

for PD. This reduction possibly resulted from that mild heart failure was considered as a complication in the present study. Although it was mild, even asymptomatic, and could be handled easily by a reduction of fluid infusion and diuretics in most cases or combined with digitalis in some cases, it is a valuable indicator of cardiac protection and restoration. Thus, it is worthy of consideration. Univariate analysis indicated that no bowel preparation, postoperative nausea and vomiting prophylaxis, early oral intake, and early and scheduled mobilization were associated with prevention of postoperative cardiovascular events. Previous studies in the field of colorectal surgery demonstrated that mechanical bowel preparation could lead to dehydration and electrolyte imbalance, especially the loss of calcium and potassium, and increasing the risk of cardiovascular events, particularly in the elderly.^[22,23] Early oral intake has been shown to be feasible and safe for PD patients.^[24] It could help reduce intravenous fluids and achieve a better fluids balance, which was believed critical to improve clinical outcomes including reducing cardiovascular events.^[25] Extended bed rest was recognized as a risk factor for unwanted cardiovascular effects a long time ago.^[26]

Intestinal dysbacteriosis was also significantly reduced after ERAS implementation and was not reported in the previous studies. Mounting evidence showed that establishing and maintaining beneficial interactions between the host and its associated microbiota were key requirements for host health.^[27,28] A common and direct result of gut microbiota disturbance in clinical practice is severe diarrhea. Therefore, it is essential to take it into consideration. In addition to avoidance of mechanical destruction to gut microbiota, such as mechanical bowel preparation, and early resumption of gut microenvironment, an optimal pain control might also contribute to prevention of intestinal dysbacteriosis.^[29]

Table 6**Uni- and multivariate analyses for weight loss***

Valuables	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Vascular resection	5.20 (1.42–19.04)	.01	6.01 (1.45–24.90)	.01
No bowel preparation	0.21 (0.07–0.65)	.006	0.19 (0.06–0.64)	.007
PONV prophylaxis	0.31 (0.10–0.94)	.04		
Early oral liquids	0.21 (0.07–0.65)	.006		

CI = confidence interval, OR = odd risk, PONV = postoperative nausea and vomiting.

* All the baseline variables and core protocol elements are considered, and only those with $P < .1$ are listed. Step methods, forward LR; C statistics, .76; P value for Hosmer–Lemeshow test, >.99.

The incidences of other complications and readmission were similar between groups in line with preceding studies,^[8] suggesting the safety of ERAS in PD. A study with 252 patients in each group reported reduced DGEs after implementation of a similar ERAS protocol.^[30] In our study, DGE was also reduced in the ERAS group, but not significantly. This was possibly a consequence of limited sample size.

It was reported that median LOPH for PD in most high-volume centers in United States is 7 to 11 days without implementing ERAS.^[31] However, median LOPH continues to plateau at a median of about 20 days even at high-volume hospitals in China.^[6,7] It is partially due to several cultural issues, including the acceptance for early discharge, the lack of discharge disposition other than home, and the availability of home care nursing. On the contrary, the big gap indicates that a big improvement can be achieved by changing traditional concept and refining conventional care. This is crucial to China where medical resource is scarce. An ERAS pathway can be a solution.

Short-term home recovery was also surveyed. Patients in the ERAS group enjoyed much better recovery of food intake and suffered fewer weight loss. Statistically, both the improvements were associated with no bowel preparation and early oral intake. Remarkably, multivariate regression analyses implied that no bowel preparation was an independent protective factor for both food intake recovery and weight loss. Previously, a large retrospective analysis of 200 consecutive patients undergoing PD found no benefits of mechanical bowel preparation before surgery in postoperative complications and hospital stay, and the 12-month survival rates.^[32] Mechanical bowel preparation should probably be avoided or limited in the context of PD, especially in patients needing vascular resection, based on current evidence.

Several limitations of our study should be considered. First, like all before–after studies, experience obtained during the study could have an impact on postoperative outcomes. However, currently, no randomized controlled trials comparing ERAS programs with traditional care in pancreatic surgery have been reported. This is probably because the ERAS program is a multimodal approach involving various interventions and professionals, and several protocol elements of an ERAS program have already become a standard practice.^[8] A before–after study may be the most practicable and effective approach. Second, limited to the follow-up data available, the sample size was relatively small. But the 2 groups were robustly matched and all the data concerning outcomes were prospectively collected. Third, as no blinding was performed and patients in the ERAS group were informed that they were undergoing an ERAS program, the Hawthorne effect was inevitable.

In conclusion, in this before–after cohort of patients undergoing elective PDs, patients in the ERAS group experienced shorter postoperative hospital stay, fewer cardiovascular complications and intestinal dysbacteriosis in hospital, and better recovery of food intake and fewer weight loss at home in the short term than those in the pre-ERAS group. The long-term influence of ERAS on these patients is under investigation.

Acknowledgments

We thank QZ for his suggestion on data analysis and manuscript organization, and MZ and JW for data verification and data input. These contributors are from our department. We appreciate all the colleagues in our center for their significant supports.

References

- [1] Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* 2008;248:189–98.
- [2] Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Brit J Anaesth* 1997;78:606–17.
- [3] Dorcaratto D, Grande L, Pera M. Enhanced recovery in gastrointestinal surgery: upper gastrointestinal surgery. *Digest Surg* 2013;30:70–8.
- [4] Van Dam R, Hendry P, Coolsen M, et al. Initial experience with a multimodal enhanced recovery programme in patients undergoing liver resection. *Br J Surg* 2008;95:969–75.
- [5] Lassen K, Coolsen MM, Slim K, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. *Clin Nutr* 2012;31:817–30.
- [6] Ke S, Ding XM, Gao J, et al. A prospective, randomized trial of Roux-en-Y reconstruction with isolated pancreatic drainage versus conventional loop reconstruction after pancreaticoduodenectomy. *Surgery* 2013;153:743–52.
- [7] Huang X, Liang B, Zhao XQ, et al. The effects of different preoperative biliary drainage methods on complications following pancreaticoduodenectomy. *Medicine (Baltimore)* 2015;94:e723.
- [8] Coolsen MM, van Dam RM, van der Wilt AA, et al. Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on pancreaticoduodenectomies. *World J Surg* 2013;37:1909–18.
- [9] Kagedan DJ, Ahmed M, Devitt KS, et al. Enhanced recovery after pancreatic surgery: a systematic review of the evidence. *HPB (Oxford)* 2015;17:11–6.
- [10] Bai X, Zhang Q, Gao S, et al. Duct-to-mucosa vs invagination for pancreaticojejunostomy after pancreaticoduodenectomy: a prospective, randomized controlled trial from a single surgeon. *J Am Coll Surg* 2016;222:10–8.
- [11] Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.
- [12] Kuppahally S, Al-Khaldi A, Weisshaar D, et al. Wound healing complications with de novo sirolimus versus mycophenolate mofetil-based regimen in cardiac transplant recipients. *Am J Transplant* 2006;6 (5 Pt 1):986–92.
- [13] Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients. *Eur Heart J* 2006;27:330–7.
- [14] Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309–32.
- [15] Soldatos CR, Dikeos DG, Paparrigopoulos TJ. Athens Insomnia Scale: validation of an instrument based on ICD-10 criteria. *J Psychosom Res* 2000;48:555–60.
- [16] Paddison JS, Sammour T, Kahokehr A, et al. Development and validation of the Surgical Recovery Scale (SRS). *J Surg Res* 2011;167:e85–91.
- [17] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–55.
- [18] MacCaffery M, Beebe A. *Pain: Clinical Manual for Nursing Practice*. Saint Louis, MO: Mosby; 1989.
- [19] Bangalore S, Guo Y, Samadashvili Z, et al. Everolimus-eluting stents or bypass surgery for multivessel coronary disease. *N Engl J Med* 2015;372:1213–22.
- [20] Hilal MA, Di Fabio F, Badran A, et al. Implementation of enhanced recovery programme after pancreatoduodenectomy: a single-centre UK pilot study. *Pancreatol* 2013;13:58–62.
- [21] Joliat GR, Labgaa I, Petermann D, et al. Cost-benefit analysis of an enhanced recovery protocol for pancreaticoduodenectomy. *Br J Surg* 2015;102:1676–83.
- [22] Holte K, Nielsen KG, Madsen JL, et al. Physiologic effects of bowel preparation. *Dis Colon Rectum* 2004;47:1397–402.
- [23] Jung B, Pählman L, Nyström PO, et al. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. *Br J Surg* 2007;94:689–95.
- [24] Lassen K, Kjaeve J, Fetveit T, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. *Ann Surg* 2008;247:721–9.
- [25] Tambyraja LA, Sengupta F, MacGregor BA, et al. Patterns and clinical outcomes associated with routine intravenous sodium and fluid administration after colorectal resection. *World J Surg* 2004;28:1046–52.
- [26] Convertino VA. Cardiovascular consequences of bed rest: effect on maximal oxygen uptake. *Med Sci Sports Exerc* 1997;29:191–6.
- [27] Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. *Nature* 2012;489:242–9.
- [28] Sommer F, Bäckhed F. The gut microbiota—masters of host development and physiology. *Nat Rev Microbiol* 2013;11:227–38.
- [29] Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. *Nat Rev Gastroenterol Hepatol* 2009;6:306–14.
- [30] Balzano G, Zerbi A, Braga M, et al. Fast-track recovery programme after pancreaticoduodenectomy reduces delayed gastric emptying. *Br J Surg* 2008;95:1387–93.
- [31] Biedermann L, Zeitz J, Mwinji J, et al. Smoking cessation induces profound changes in the composition of the intestinal microbiota in humans. *PLoS One* 2013;8:e59260.
- [32] Lavu H, Kennedy EP, Mazo R, et al. Preoperative mechanical bowel preparation does not offer a benefit for patients who undergo pancreaticoduodenectomy. *Surgery* 2010;148:278–84.