

Brief communication

Fast-track recovery after major liver and pancreatic resection utilizing the ERAS approaches: A meta-analysis

Junfen Shi, Fang Li*

Abstract

Background: Enhanced Recover After Surgery (ERAS) is a multidisciplinary multimodal approach used to treat surgical patients, which targets perioperative management optimization of results. This approach was first applied to patients who had undergone colorectal surgery. However, its application on pancreaticoduodenectomy patients is limited. Currently numerous studies conducted around ERAS for pancreaticoduodenectomy patients have been published. This study collected data comprehensively in order to indicate the best indication summary for the clinic.

Objective: With the help of this study, the practicality and safety of the ERAS approach was assessed in terms of recovery after surgery in the pancreaticoduodenectomy patient at the time of the perioperative supervision.

Methods: Literature searches were conducted in databases such as Embase, Cochrane, and PubMed online databases, published up until July 2020. Case-control studies and randomized controlled trials (RCTs) that applied ERAS for pancreaticoduodenectomy patients were included. The patients were divided into two parts: the ERAS group and the control group. Revman 5.3 software and R software were utilized for all statistical analyses. The results were calculated as weighted mean differences or odds ratios with a 95% confidence interval for publication bias assessment funnel plots. Sensitivity and subgroup analyses were performed to investigate the source of heterogeneity.

Results: A total of 3613 patients from 20 studies (1699 control group patients vs. 1914 ERAS group patients) were included in the study. Among the 20 studies, 16 studies were case-control, and 4 were RCTs. The results indicated that, ERAS approached patients suffered less from postoperative complications as compared to the control group. ERAS group patients had fewer gastric symptoms, and they also had less hospital stay.

Conclusion: It has been found that the ERAS treatment method is highly beneficial and safe for treating pancreaticoduodenectomy patients. This method results in a speedy recovery as compared to the other methods. [*Ethiop. J. Health Dev.* 2021;35(4): 344-348]

Keywords: ERAS, Pancreatoduodenectomy, Surgical patients, Fast-track recovery.

Introduction

In 1997 Kehlet et al. first proposed enhanced recovery after surgery (ERAS) from the University of Denmark Copenhagen (1). Enhanced recovery after surgery is a multidisciplinary, multimodal evidence-based approach for the care of surgical patients. ERAS method has been widely accepted globally. Pancreatoduodenectomy is often considered the most challenging procedure in surgery. In recent years, multiple studies on the ERAS program have been carried out globally among patients undergoing the Pancreatoduodenectomy. According to these studies, ERAS implementations on pancreaticoduodenectomy patients are efficient and prove to be a safe approach for postoperative recovery. The randomized control trials for accumulation of good quality case-control studies motivate for improving the analysis. This study collected evidence in support of the best treatment practices for the clinic.

Material and Method

A literature survey on different websites and data sources such as Embase, PubMed, and, Cochrane online library search was conducted in order to collect case studies that investigate the ERAS approach of perioperative patients who had undergone the Pancreatoduodenectomy, from studies which were conducted from July 2019 to July 2020. The search terms used were as follows: "ERAS," "Pancreatoduodenectomy," "Pancreatectomy," "enhanced recovery after surgery," "fast track surgery,"

"FTS," "accelerated recovery surgery," "rapid recovery surgery," "critical pathway." The search strategies and details are listed in Table 1.

Inclusion Criteria:

Study types: Case-control studies or randomized control trials, with language, restricted to English.

Members of study: Patients were below 18 years of age. They had undergone elective pylorus-preserving pancreaticoduodenectomy, and patients who underwent a whipple procedure irrespective of the patients' nationality.

Interventions: If patients received ERAS preoperative approaches then they were included in the experimental group, and the patients who received the traditional treatment procedures were included in the control group. As per the guidelines for the perioperative pancreaticoduodenectomy patients' care issued in the 2012, a minimum 9 out of the 27 recommendations were implemented in the ERAS group.

Exclusion criteria:

Article full text was not available
Republished article
Palliative surgery which focused on laparoscopic surgery or emergency surgery.
Study quality which was 13 according to the MINORS
Outcomes which were available.

* Affiliated Hospital of Inner Mongolia Medical University, Department of Liver, Gallbladder, Pancreatic and Spleen, Inner Mongolia, China, 010050. Email:shijf3762@gmail.com

Data extraction and assessment of data quality

Two researchers investigated and extracted the data individually. The information extracted from the study included publication year, surgery type, demographic data, interventions, outcomes, ERAS patients number, and the control group number, etc. Two researchers evaluated the article quality independently, and the differences were addressed through discussions and consultation with a third researcher. The randomized trial quality was assessed using the Cochrane risk assessment tool, and the case-control study quality was evaluated with the help of the methodological index for non-randomized trials.

The outcome of interest

The primary outcome of the research was the postoperative complications, with minor complications such as, delayed gastric emptying, pancreatic fistula, abdominal abscess, incision infections morbidity, and the length of hospital stay. International Pancreatic Fistula Study groups definition of the pancreatic fistula was used in the study, described as the drain output of any measurable fluid volume containing Amylase three days postoperative. At the same time, delayed gas emptying is defined as maintaining a Nano gastric tube for less than three days, determined by the International Study of Pancreatic Surgery. Postoperative vomiting for three days with Nano gastric tube or being unable to take in solid food for seven days. Hospital stay length referred to the period between the surgery date and the discharge date. The overall postoperative complications include any problems during the 30 days from the surgery up to the discharge, and the Clavien-Dindo system was used for gradation of the

severity into the three like categories, such as, significant, moderate, and minor complications. Readmission was defined as admission within 30 days after discharge. Reoperation was defined as an operation which occurs within the 30 days after release, and mortality rate was defined as the death which occurred within the 30 days after discharge.

Statistical analysis

The statistical analysis was performed using the R software and the Revman 5.3 software. The outcomes were calculated using the Odds ratio or the weighted mean differences with their corresponding 95% CI (confidence intervals). While the heterogeneity was analyzed through the use of the chi-squared test, with the $\alpha=0.05$ and the I^2 test was used to measure the heterogeneity. Subgroup analysis was performed to analyze only the western countries. For the eastern countries and the RCT or randomized controlled trials, case-control studies were used to explore the probable source of the heterogeneity.

Results

According to the search strategy, the total of retrieved records from the online databases was 345, up until July 2020. After duplicates were removed, 281 records were left, and 235 articles were excluded following the title and abstract review. After studying the leftover 46 papers, 26 were removed for different reasons. Following the extractions a total of 20 articles are retained for further analysis and included in the study. A flow chart of the inclusion strategy containing the 3613 patients and the 20 articles are provided below (Figure 1). The quality assessments and characteristics of the included articles are summarized in Table 1.

Table 1: Quality assessment Characteristics and of the included studies

Outcome of interest	No. of studies	OR/WMD	No. of patients	95% CI	Heterogeneity P-value	P-value	$I^2\%$
western countries study							
DGE	12	0.56	1850	0.43-0.73	0.43	<0.0001	1
Mortality	13	0.95	2059	0.56-1.61	0.99	0.84	0
PF	12	0.89	1850	0.71-1.13	0.85	0.35	0
Overall morbidity	12	0.68	1983	0.56-0.82	0.46	<0.0001	0
Readmission	12	0.99	1898	0.72-1.38	1	0.97	0
LOS	3	-3.3	491	-5.17, -1.44	0.06	0.0005	63
Reoperation	8	0.92	1457	0.63-1.34	0.86	0.67	0
Eastern countries study							
PF	6	0.76	1307	0.46-1.27	0.008	0.3	68
LOS	5	-4.36	1194	-4.93, -3.79	0.005	<0.00001	73
DGE	6	0.44	1307	0.32-0.62	0.77	<0.00001	0
Overall morbidity	6	0.54	1395	0.39-0.74	0.17	<0.00001	36
Mortality	7	0.67	1554	0.43-1.03	0.86	0.07	0
Reoperation	4	2.88	655	0.99-8.41	0.99	0.05	0
Readmission	6	1.12	1492	0.75-1.66	0.39	0.58	4
Case-control studies							
PF	15	0.85	2848	0.70-1.04	0.38	0.11	7
Overall morbidity	16	0.62	3057	0.52-0.73	0.31	<0.00001	13
DGE	15	0.53	2848	0.43-0.61	0.5	<0.0001	0
Mortality	16	0.77	3057	0.55-1.07	0.99	0.12	0
LOS	6	-4.46	891	-5.08, -3.83	0.001	<0.00001	75
Reoperation	10	0.96	1706	0.66-1.38	0.89	0.82	0
Readmission	14	1.01	2834	0.77-1.31	0.98	0.96	0
RCT							
PF	3	0.91	309	0.30-2.79	0.03	0.87	72
Reoperation	2	3.21	406	0.86-12.03	0.96	0.08	0
DGE	3	0.41	309	0.24-0.71	0.66	0.002	0
LOS	2	-3.71	794	-4.80, -2.62	0.83	<0.00001	0

Overall morbidity	2	0.52	321	0.17-1.62	0.07	0.26	71
Readmission	4	1.24	556	0.64-2.39	0.38	0.52	2

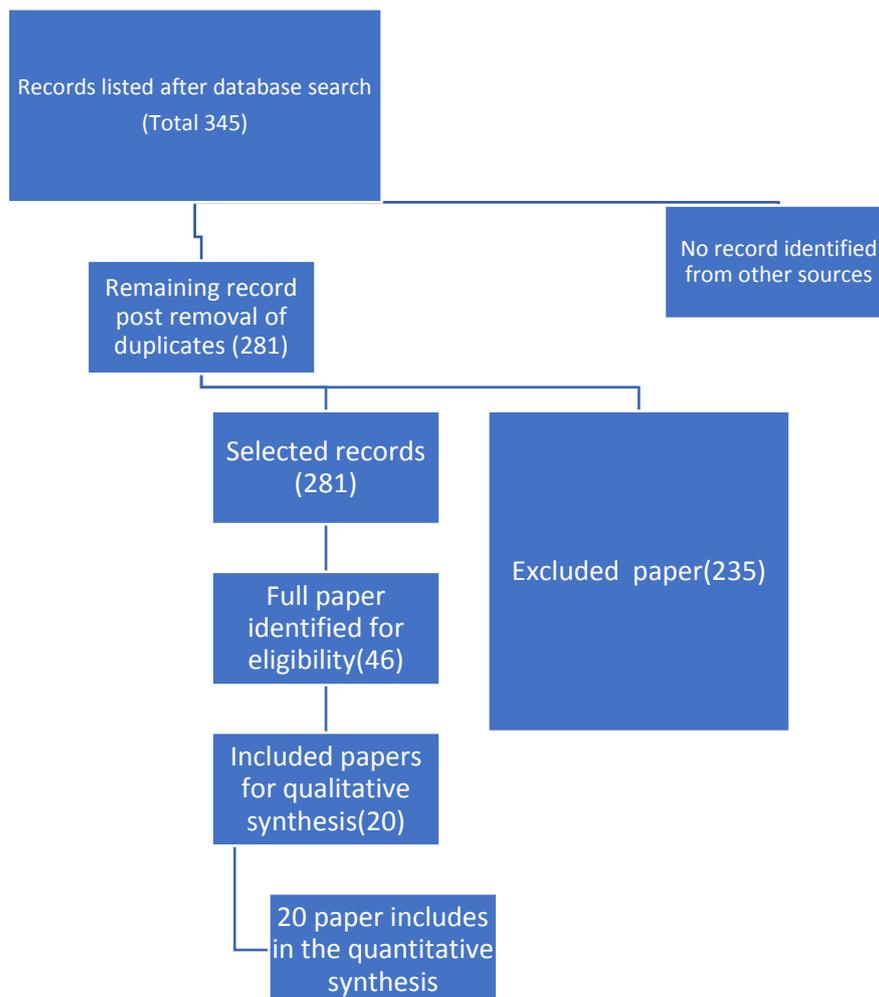


Figure 1: **PRISMA flow diagram of the included studies for meta-analysis**

Primary outcome

A total of 20 articles were included in the analysis. Following the metanalysis it has been found that postoperative problems were significantly lower in the ERAS group (OR = 0.60, 95% CI: 0.53- 0.73, P-value< 0:00001). Additionally, the 13 types of research were categorized as the postoperative complication indication based on the Clavien- Dindo definitions. While the postoperative complications were less in the ERAS group as compared to the control group (OR = 0.71, 95% CI: 0.59-0.87, P-value = 0:0005). Also, there was no significant difference between the moderate and the severe problems for both groups (Clavien- Dindo III-IV; OR= 1.05, 95% CI= 0.81-1.42, P=0.68).

Other outcomes

A total of 20 studies were reported for the Pancreatic fistula. There was no significant differences between the ERAS treated group and the control group(Odd Ratio = 0.87, 95% CI: 0.68-1.07, P =0.16). Furthermore, the 13 types of research were subdivided among the different grades according to the severity of

the Pancreatic fistula. The combined analysis also indicated no differences between the Grade 'A,' Grade ' B,' and Grade ' C' pancreatic fistulas between the two groups.

Delayed gastric emptying was lower in the ERAS group as compared to the control group (Odd Ratio = 0.52, 95% CI: 0.41-0.62, P < 0:00001). Hospital stay length for the ERAS group was shorter(WMD = -4.26, 95% CI: -4.8~-3.72, P < 0:00001). The wound infection rate, abdominal abscess, and reoperation rates indicate that morbidity rates had no significant changes in the two groups. Subgroup analysis was performed in the western countries' RCT and the case-control cases. Due to the insufficient RCT numbers, their group produces inconsistent outcomes as compared to the other groups. The overall postoperative complications, pancreatic fistulas, and mortality rates, and the delayed gastric emptying data were taken in order to evaluate publication bias. Results of the subgroup analyses are presented in Table 2. The drawn funnel plot indicated the publication bias as a minimum impact on the meta-analysis.

Table 2: Subgroup analysis results

Country	Control group	ERAS group	Total	MINORS score
United States	42	92	135	15/24
Italy	252	252	504	15/24
Netherlands	97	86	183	15/24
United States	64	145	209	13/24
Korea	124	123	247	*
Britain	24	20	44	14/24
China	83	76	159	*
Japan	90	100	190	13/24
Britain	65	65	130	14/24
Switzerland	87	74	161	15/24
Italy	115	115	230	18/24
China	31	31	62	15/24
China	310	325	635	14/24
Japan	37	37	74	*
Spain	44	41	85	16/24
China	63	124	187	15/24
Greece	50	75	125	16/24
Sweden	50	50	100	16/24

Discussion

Pancreaticoduodenectomy is the only potential treatment to cure a malignant tumor. ERAS is a multidisciplinary, multimodal approach for surgical patient care, aiming for perioperative management and outcome optimization. The central concept of the ERAS is a reduction in patients' fasting period, providing the preoperative carbohydrate treatment, serving multimodal analgesia, administration of the goal oriented fluid therapy, early extubation promotion, implementation of the early mobilization for patients surgical stress response reduction and also reducing the hospital stay duration. ERAS requires multidisciplinary collaboration among the surgery departments, anesthesia, nutrition, nursing, and rehabilitation. This meta-analysis included 20 studies from 2019, in order to investigate the efficacy of ERAS for patients undergoing Pancreaticoduodenectomy. As compared to previous meta-analyses, this study included many randomized control trials, so a significant number of medical studies supports this result. The ERAS group baseline characteristics and control groups were constant in this research, which included strict inclusion and exclusion criteria. All the studies were included based on the standardized definition for the result. There was significantly less heterogeneity in most outcome observations. According to this research, ERAS can decrease postoperative complications, including minor complications. The moderate and severe complication incidents and the pancreatic fistula incidents of the incision infections and abdominal abscess incidents are not significantly different between the two groups. In five articles, the patient's obedience was mentioned. According to Bragg et al. (2), the intra and preoperative compliance with the ERAS items were higher. While in the postoperative ERAS, the patient's compliance was relatively low. The subgroup analysis result indicate that the patients without complications have shown better adherence as compared to the patients with complications. According to Bai et al., the preoperative compliance

with the ERAS core elements were more than the postoperative compliance (3).

In comparison, Zourous reported (4) no complications and/or minor complications for patients who had a compliance rate of 74 to 100% as they had a high degree of adherence in the ERAS group with a decreased hospital stay. While Takagi et al. (5) found that 84% of patients follow the ERAS protocol while 30% of patients follow the postoperative pathway of the ERAS treatment. Wong et al. (6) found that the ERAS protocol for postoperative patients is not promising. About 2352 patients surveyed, who were treated with the ERAS protocol showed a high compliance rate associated with a decreased postoperative complication rate (7) and shorter hospital stays. Therefore, patients compliance improvement is necessary to ensure that ERAS should be executed in practice. Several limitations of this analysis need to be mentioned. The study's primary end is the preliminary study in this paper; included are retrospective case-control studies, which can lead to recall and selection bias. This can also result in measurement and implementation bias. The second limitation of the study is that ERAS protocols vary from 9 to 25 items within the different study reports, and patient compliance is tough to control, which may lead to clinical heterogeneity. The ERAS protocol implementation method is not practicable. This primary cause for the previous meta-analysis only includes the case-control reports and the significant aspects that directed the moderate RCT quality in this study.

Conclusion

It has been concluded that the ERAS method is very safe and effective in pancreatoduodenectomy patients management. This approach can also accelerate postoperative recovery. This also promoted better treatment as compared to the gastrointestinal function which reduced hospital stay. Further research is required for solid evidence on this topic. Recently

ERAS strategies in many areas promote the minimum invasive surgery selection, and as the laparoscopy procedure for the Pancreaticoduodenectomy is developing in hepatobiliary surgery, we look for more study for the reports ERAS application for patients of LPD. Therefore, ERAS is needed to confirm that each thing is implemented, provide specific and individual patients care, improve patient's compliance and recovery.

Reference

1. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *British journal of anaesthesia*. 1997 May 1;78(5):606-17.
2. Braga M, Pecorelli N, Ariotti R, Capretti G, Greco M, Balzano G, Castoldi R, Beretta L. Enhanced recovery after surgery pathway in patients undergoing Pancreaticoduodenectomy. *World journal of surgery*. 2014 Nov;38(11):2960-6.
3. Bai X, Zhang X, Lu F, Li G, Gao S, Lou J, Zhang Y, Ma T, Wang J, Chen W, Huang B. The implementation of an enhanced recovery after surgery (ERAS) program following pancreatic surgery in an academic medical center of China. *Pancreatology*. 2016 Jul 1;16(4):665-70.
4. Zouros E, Liakakos T, Machairas A, Patapis P, Agalianos C, Dervenis C. Improvement of gastric emptying by enhanced recovery after Pancreaticoduodenectomy. *Hepatobiliary & Pancreatic Diseases International*. 2016 Apr 1;15(2):198-208.
5. Takagi K, Yoshida R, Yagi T, Umeda Y, Nobuoka D, Kuise T, Hinotsu S, Matsusaki T, Morimatsu H, Eguchi J, Wada J. Effect of an enhanced recovery after surgery protocol in patients undergoing Pancreaticoduodenectomy: a randomized controlled trial. *Clinical Nutrition*. 2019 Feb 1;38(1):174-81.
6. Wong-Lun-Hing EM, Van Dam RM, Heijnen LA, Busch OR, Terkivatan T, van Hillegersberg R, Slooter GD, Klaase J, de Wilt JH, Bosscha K, Neumann UP. Is current perioperative practice in hepatic surgery based on enhanced recovery after surgery (ERAS) principles?. *World journal of surgery*. 2014 May;38(5):1127-40.
7. Group EC. The impact of enhanced recovery protocol compliance on elective colorectal cancer resection: results from an international registry. *Annals of surgery*. 2015 Jun;261(6):1153-9.