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Enhanced recovery after surgery protocol enhances early postoperative recovery after pancreaticoduodenectomy

Ramasamy Mahendran[a], Mallika Tewari[a,*], Vinod Kumar Dixit[b], Hari Shankar Shukla[a]

[a] Department of Surgical Oncology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP 221005, India
[b] Department of Gastroenterology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP 221005, India

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ABSTRACT

Background: Enhanced recovery after surgery (ERAS) protocol is a multimodal, multidisciplinary and evidence-based approach to reduce surgical stress and enhance recovery in the postoperative period. This study aimed to analyze the outcome of ERAS protocol in patients after pancreaticoduodenectomy (PD).
Methods: A total of 50 consecutive patients with pancreatic/periampullary cancer who underwent PD between January 2016 to August 2017 were included in the study. As per the institute ERAS protocol, nasogastric tube (NGT) was removed on postoperative day (POD) 1 if output was less than 200 mL and oral sips were allowed; oral liquids were allowed on POD2; semisolid diet by POD3; abdominal drain was removed on POD 4 if output was less than 100 mL with no evidence of postoperative pancreatic fistula (POPF); normal diet was allowed on POD5. Discharge criteria on POD6 were afebrile, tolerating oral normal diet, pain free and no surgery related complications (defined as per the ISGPS definitions).
Results: NGT was removed on POD1 in 45 (90%) patients, abdominal drain removed by POD4 in 41 (82%) and 43 (86%) patients were discharged on POD6. There was no 30-day postoperative mortality. Three (6%) patients had delayed gastric emptying (DGE). None had postoperative hemorrhage and POPF. Readmission rate was 8%. A significant relation was found between the length of hospital stay (LOS) with age ($P < 0.05$) and a marginal relation between LOS and postoperative albumin ($P = 0.05$).
Conclusions: ERAS protocol can be safely followed in the perioperative care of patients who undergo PD. Early removal of NGT and allowing oral diet restore bowel function early. ERAS decreases the LOS and postoperative complications.

Introduction

Enhanced recovery after surgery (ERAS) protocol or fast-track protocol was introduced first in 1997 by Kehlet [1]. It was built on the concept that postoperative recovery is related to preoperative assessment, intraoperative fluid replacement, surgical technique, type of anesthesia, postoperative pain control, comorbidities and nutritional status [2]. The main principle of ERAS protocol is to decrease the surgical stress response which in turn prevents the immunosuppression. Other components of ERAS protocol like decreasing postoperative pain, avoiding blood transfusion, avoiding hypothermia also prevent tumor seeding and recurrence [3].

The average length of hospital stay (LOS) after colorectal surgery has decreased to 4 days by following ERAS protocol [4]. Similar promising studies have been reported after gynecological, breast, liver, urological, gastric and bariatric surgeries [5–9]. However, only limited studies are available worldwide regarding application of the ERAS protocol after pancreaticoduodenectomy (PD) [10–12]. PD is an accepted surgical procedure in the management of pancreatic and periampullary cancer (PAC) and is beset with complications owing to complexity of the procedure. Mortality rate after PD has dropped to 1%–2% though morbidity rates remain as high as 30% in experienced centers [13–15]. Therefore, many surgeons prefer a conservative approach in the postoperative period after PD. Conventional perioperative protocol for PD includes removal of nasogastric tube (NGT) on postoperative day (POD) 4 and drain removal by POD 7. The average LOS in a patient with conventional preoperative care protocol ranges from 11 to 15 days [16]. This leads to an increase in health care costs and bed occupancy [17].

The present study aimed to analyze the outcome of ERAS protocol after PD in our hospital.

* Corresponding author.
E-mail address: drmtewari@gmail.com (M. Tewari).

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Table 1
Perioperative ERAS protocol followed in our study.

Perioperative day	Perioperative protocol
Day before surgery	Clear liquids till 4 h before surgery
	No mechanical bowel preparation
POD0	Preoperative antibiotic
	Epidural catheter
	Central line
	Foleys catheter
	Sequential compression device
	Somatostatin analogues (octreotide)
	Mobilisation: sitting up on bed
	Restrictive fluid
POD1	NGT removal if output < 200 mL
	Oral sips of clear liquids
	Ambulation at least 3 times
	Intensive spirometry
	Steam inhalation
	Chest physiotherapy
POD2	Clear liquid diet
	Ambulation increased to 6 times
	IV fluid support based on intake
	Removal of central line
	Removal of urinary catheter
	Removal of epidural catheter after medication
POD3	Oral semisolid diet
	Decrease in dose of IV analgesia
	Stop IV support if intake more than 1500 kcal and 1 L fluid intake
POD4	Drain fluid amylase
	Drain removal if output < 100 mL and no features suggestive of POPF
	All medication stopped except oral proton pump inhibitors, metoclopramide, multivitamin
POD5	All IV access removal
	Oral medications
	Normal diet
POD6	Plan for discharge
	Date for next visit

POD: postoperative day; NGT: nasogastric tube; IV: intravenous.

Methods

Patients

Our study was a prospective, single arm interventional hospital-based study conducted in the Hepato-Pancreato-Biliary & Gastrointestinal Division, of a tertiary care hospital, from January 2016 to August 2017. A total of 50 consecutive patients with PAC/pancreatic head cancer who underwent PD were included in the study. An institute ERAS protocol (Table 1) for perioperative care of PD patients was developed based on guidelines by ERAS society published in 2012 [18].

Patients were put on clear liquid diet for two days prior to surgery. No mechanical bowel preparation was used. Patients were given antianxiety medication by the anesthesia team. Central venous catheter and thoracic epidural catheter were placed in all patients prior to surgery. Sequential compression device was used throughout the course of surgery. Broad spectrum antibiotic prophylaxis was given within 1 h before the time of incision. Hypotensive anesthesia and restrictive fluid policy was preferred throughout the course of surgery. Blood transfusion was not preferred if hemoglobin > 8 mg/dL. No pharmacological deep vein thrombosis (DVT) prophylaxis was given. Patients were mobilized on POD 1 at least 3 times and were encouraged to take oral liquids. Drain fluid and serum amylase levels were checked on POD4. Drain removal criteria was drain output less than 100 mL/day and drain amylase level not suggestive of postoperative pancreatic fistula (POPF) (less than three times the upper limit of normal serum amylase) as per International Study Group of Pancreatic Surgery (ISGPS) guidelines [19]. All complications were defined as per the ISGPS criteria including delayed gastric emptying (DGE) [20], post pancreatectomy hemorrhage [21] and graded as per Clavin-Dindo classification [22]. Discharge criteria were patients tolerating normal diet, afebrile, pain free, independent mobility and no requirement for intravenous (IV) fluids. All surgical procedures were performed by a single experienced surgeon. All patients were planned for surgery after adequate preoperative optimization and were American Society of Anesthesiologists (ASA) class 1 or 2.

All patients were staged by a triphasic pancreatic protocol computed tomography scan within 1 month prior to surgery. A side-viewing upper gastrointestinal endoscopy and biopsy was also performed. In a few patients endoscopic ultrasound (EUS)-guided biopsy was done prior to surgery. Preoperative biliary drainage was not performed as a routine unless for a specific indication like cholangitis or delay in surgery for over 2 weeks. Patients were started on preoperative chest physiotherapy. A detailed history obtained from the patients was recorded on a predesigned proforma. Patient demographics, investigations and daily progress of patients were collected. Patients were followed up from the day of discharge from the hospital till the end of study. Any event like readmission within one month of discharge were recorded and included in the analysis. An informed consent was taken from each patient. The study was approved by the Institute's Ethical Committee.

Statistical analysis

A comparative analysis was performed on patient-related factors versus outcome in the study: age, comorbidities, preoperative biliary stenting, postoperative serum albumin and postoperative complications versus LOS. Statistical analysis was performed using SPSS (version 16.0, Chicago IL, USA) software. Chi-square test was used to find the association between two categorical variables. A P value of < 0.05 was considered statistically significant.

Table 2
Demographic factors.

Demographic factors	Data
Age	50.7 ± 10.0
≤ 50 yr	28 (56%)
> 50 yr	22 (44%)
Sex	
Male	41 (82%)
Female	9 (18%)
Comorbidities	
Diabetes	4 (8%)
Hypertension	5 (10%)
Presenting features	
Jaundice	35 (70%)
Fever	6 (12%)
Pain abdomen	7 (14%)
Malena	2 (4%)
Preoperative biliary drainage	
Nil	22 (44%)
Stenting	28 (56%)
Plastic	28 (56%)
Metallic	0
Location of tumor	
Ampulla of vater	38 (76%)
Duodenum	3 (6%)
CBD	2 (4%)
Pancreatic head	7 (14%)
Perioperative albumin (mg/dL)	
Preoperative	3.6 ± 0.8
< 3	15 (30%)
≥ 3	35 (70%)
Postoperative	3.1 ± 0.5
< 3	31 (62%)
≥ 3	19 (38%)
Surgery	
PRPD	49 (98%)
PRPD + portal vein	1 (2%)
Resection	
DMPJ	46 (92%)
PG	4 (8%)
Operative time (min)	230 (220 – 280)
Blood loss (mL)	160.0 ± 40.0

Data were expressed as mean ± SD, median (range) or number (percentage). PRPD: pylorus resecting pancreaticoduodenectomy; DMPJ: duct to mucosa pancreaticojejunostomy; PG: pancreaticogastrostomy.

Table 3
Postoperative outcomes.

ERAS postoperative targets	Proportion of patients achieved postoperative targets
NGT removal on POD1	45 (90%)
Oral sips on POD1	45 (90%)
Oral liquid diet on POD2	45 (90%)
Urinary catheter removal on POD2	44 (88%)
Epidural catheter removal on POD2	47 (94%)
IV fluid stopped on POD 3	41 (82%)
Drain removed on POD 4	41 (82%)
Tolerating normal diet on POD5	47 (94%)
Discharge on POD6	43 (86%)

NGT: nasogastric tube; POD: postoperative day; IV: intravenous.

Results

The demographic, preoperative and postoperative factors of 50 consecutive patients who underwent PD are shown in Table 2. The mean age of patients in our study was 50.7 ± 10.0 years ranging from 28 to 70 years. Thirty-five (70%) patients presented with jaundice. Preoperative biliary stenting was done in 28 (56%) patients for cholangitis and/or delay in surgery for more than 2 weeks. Ampulla was the most common location of tumor in this study comprising 38 (76%) patients. The mean preoperative albumin of patients was 3.6 ± 0.8 mg/dL ranging from 1.9 to 6.2 mg/dL. Patients with preoperative albumin < 3 mg/dL were optimized with high protein enteral feeding for 2 weeks prior to surgery. The mean postoperative albumin of patients was 3.1 ± 0.5 mg/dL ranging from 2.0 to 4.0 mg/dL. All 50 patients underwent pylorus resecting pancreatoduodenectomy (PRPD). One patient underwent PRPD with segmental resection of portal vein and end to end anastomosis.

Table 4
Readmission.

Day of discharge	Day of readmission	Reason	Management
POD 6	POD 21	Burst abdomen	Secondary suturing
POD 15	POD 24	Dehydration	Conservative
POD 18	POD 28	Wound infection	Conservative
POD 8	POD 18	Wound infection	Conservative

POD: postoperative day.

Table 5
Postoperative complications.

Major Complication	No. of patients	Clavien-Dindo grade
DGE	3 (6%)	2
POPF	0	0
PPH	0	0
Wound-related complication	3 (6%)	2
	1 (2%)	3

DGE: delayed gastric emptying; POPF: postoperative pancreatic fistula; PPH: post-pancreatectomy hemorrhage.

The postoperative outcomes of the patients are summarized in Tables 2–5. All patients were mobilized to sit on the day of surgery. Forty-six (92%) patients were mobilized out of bed at least 3 times on POD1. One patient had a history of traumatic fracture femur 2 weeks before surgery and was kept on immobilization. Forty-five (90%) patients had their NGT removed on POD1. Forty-five (90%) patients tolerated liquid diet on POD2. Forty-seven (94%) patients tolerated normal diet on POD5. DGE was observed in 3 (6%) patients (Table 5); 1 patient had ISGPS grade B and 2 had grade C DGE. There was no POPF as per the ISGPS definition. Abdominal drain was removed in 41 (82%) patients on POD4. In the other 9 patients, drain was removed a few days later as drain output was more than 100 mL/day (amylase and drain amylase levels were normal). None of the patients had postoperative hemorrhage. Forty-three (86%) patients were discharged on POD6. Overall, the average LOS was 7.38 ± 4.28 days.

Twenty-seven patients ≤ 50 years age, as compared to 16 who were > 50 years age, were discharged by POD6. The association between age and LOS was found to be statistically significant ($P < 0.05$). All 5 patients with hypertension and 4 with diabetes mellitus were discharged on POD 6. The association between history of hypertension, diabetes mellitus, respiratory problems, body mass index and the LOS was not statistically significant. Similarly, there was no statistically significant association between preoperative biliary drainage and LOS ($P = 0.2$). Out of 7 patients discharged after POD6, 3(43%) had postoperative albumin level < 3 mg/dL. A marginal significant association was found between the postoperative albumin level and the LOS ($P = 0.05$).

Four (8%) patients were readmitted within one month of surgery after discharge for wound related complications that subsided on conservative management (Table 4). Two patients presented with wound infection, 1 with burst abdomen and 1 with dehydration. Out of these 3 had Clavien-Dindo grade 2 wound infection and one had burst abdomen. Overall morbidity (Clavein-Dindo grade 3 or above) was only 1(2%). Fistula risk score was calculated as per the criteria defined by Callery et al. [23] for PD. Fifteen patients belonged to the low-risk group (score 1–2), 31 to the intermediate-risk group (score 3–6) and 4 to the high-risk group (score 7–10).

Discussion

PD is one of the most challenging abdominal operation with high morbidity and mortality rates even in high volume centers. Because of the fatal major postoperative complications, surgeons prefer a more conservative approach that leads to increase in LOS. ERAS protocol is a multimodal, multidisciplinary and evidence-based approach to reduce surgical stress and enhance recovery in the postoperative period. The ERAS programs can also be referred to as "fast-track surgery", "fast-track pathway", and "clinical pathway" [24]. Our study was different from other similar studies because only carcinoma patients were included and all surgeries were done by a single experienced surgeon. In our study, the average LOS was 7.38 ± 4.28 days with a median of 6 days with no postoperative pancreatic fistula or hemorrhage as per the ISGPS definitions. A PubMed search revealed only two studies from India on ERAS after PD [25,26]. Similar studies from various other countries reported LOS ranging from 7.5 to 11 days [26–34].

Few recent systematic reviews and meta-analysis have found ERAS protocol to be beneficial for patients undergoing PD. Xiong et al. [10] reported results of 14 non-randomized comparative studies with 1409 ERAS cases and 1310 controls. The ERAS group had a significantly shorter postoperative LOS with mean difference of 4.17 days, lower DGE (OR: 0.56; 95%CI: 0.44–0.71), overall morbidity (OR: 0.63; 95% CI: 0.54–0.74) and in-hospital costs (all $P < 0.001$) compared to those in the conventional group [10]. Lei et al. [35] conducted a computerized search in databases including PubMed, Embase, MEDLINE, Web of Science, Cochrane Library, CNKI, Wanfang and VIP for randomized controlled trials (RCTs) or clinical controlled trials (CCTs) describing an ERAS program in patients undergoing PD published between January 1966 and May 2014. Six RCTs and 8 CCTs including 2565 patients were finally selected for this study, including the study group ($n = 1366$) and the control group ($n = 1199$). ERAS group had a shorter LOS ($P < 0.05$), lower postoperative complication rate ($P < 0.05$) and lower mortality ($P < 0.05$).

An RCT published recently by Takagi et al. [34] compared outcomes of 37 patients in the control group and 37 in the ERAS group following PD. The ERAS group had significantly shorter mean LOS (20.1 ± 5.4 days vs 26.9 ± 13.5 days, $P < 0.001$), lower percentage of postoperative complications (32.4% vs 56.8%, $P = 0.034$) and readmissions (0% vs 8.1%, $P = 0.038$), significantly better quality-of-life (184 ± 12.4 vs 177 ± 14.5, $P = 0.022$) and lower (though not significant) total medical cost than those in the control group.

Thus, evidence is emerging that ERAS protocol has a significant positive impact on early postoperative recovery of patients undergoing PD. All postoperative complications in our study were grade 2 as per Clavin-Dindo classification except one burst abdomen that required secondary suturing. None of the patients had POPF or post-pancreatectomy hemorrhage and there was no 30-day postoperative mortality. Overall postoperative complications were less than previous reports [23,25] and readmission rates were similar to other reported studies [24,27,31–34].

The success of ERAS protocol depends on early tolerance of oral feed, removal of drains and mobilization. Routine use of a NGT is not recommended after PD [36,37]. Zouros et al. [29] reported that the independent effect of the ERAS protocol in reducing DGE and LOS was confirmed by multivariate analysis. Similar findings were published by Balzano et al. [27]. In our study, NGT was removed on POD1 in 90% of patients and they were started on oral liquids. Early mobilization of a surgical patient is associated with decreased risk of deep vein thrombosis, early recovery of function, psychological wellbeing, improved cardiovascular and pulmonary functions and shortening the length of hospital stay [38]. Removal of urinary catheter, adequate analgesia and motivation improves mobilization.

Mechanical bowel preparation is not practiced nowadays as there is no added benefit over clear liquids. It might even be associated with higher anastamotic leak, urinary tract infection and wound complications [39–41]. None of our patients received mechanical bowel preparation. Pharmacological DVT prophylaxis was not included in our protocol as the incidence of DVT in Indian population is low [42]. However, all our patients had sequential calf compression device during surgery. All patients were mobilized out of bed on POD1 and active limb physiotherapy was part of our ward management protocol.

Another important area of recent research is goal-directed fluid therapy (GDFT) which significantly affects the postoperative outcome of patients. Intravenous administration of more fluid results in bowel edema and raised interstitial lung water resulting in both intraoperative and postoperative complications [43,44]. Both fluid excess and dehydration in splanchnic circulation result in a delay in recovery of bowel function and may lead to acute kidney injury and pulmonary complications. Combined effects of anaesthetic agents which cause vasodilatation and hypotension along with longer operating time and blood loss in PD may result in hypoperfusion that delays the recovery of bowel function [45,46]. A prospective analysis of 350 major pancreatic resections in a pancreatic unit in Italy, revealed that liberal fluid balance was associated with an increased rate of Clavien-Dindo $\geq$ IIIB (60.3% vs. 30.2%, $P < 0.01$) and pancreatic fistula (33.3% vs. 19.9%, $P = 0.05$) after PD. However, they also cautioned that in a soft pancreas, an near-zero fluid balance could lead to pancreatic stump ischemia and anastomotic failure [47]. In our study intraoperative fluid balance was maintained with central venous pressure monitoring. Other intraoperative factors like hypothermia and hemorrhage can also affect the postoperative recovery [48,49]. Hypotensive anesthesia preferred to decrease the intraoperative blood loss and the need for blood transfusion.

Preoperative optimization of medical condition like diabetes, hypertension, smoking cessation, other endocrine abnormalities are also essential for the good postoperative outcome [47]. Drain removal criteria in our study was drain output less than 100 mL/day on POD4 and drain amylase less than three times the upper limit of normal serum amylase as per ISGPS definition. In our study 41(82%) patients met the drain removal criteria by POD4, and this was much earlier than reported by other studies (ranges from 6 to 10 days) [29–31]. Tolerating normal diet is one of the criteria for discharge in the ERAS protocol. In our study 47 (94%) patients tolerated normal diet by POD 5 which was similar to other published studies [32,33].

Demographic factors also influence the outcome of ERAS protocol. In our study, we found a statistically significant association between the age of the patient and LOS ($P < 0.05$). Of the 7 patients discharged after POD 6, 6 were above 50 years. This was contradictory to other studies that followed the ERAS protocol for perioperative care and found no association between age and LOS [26,31,32]. Controlled comorbidities like diabetes and hypertension had no significant association with discharge and it is well proven in various studies [50]. Preoperative biliary drainage had no association with the early discharge but it can cause an increased rate of wound infection [51,52]. We found a marginal association with immediate postoperative albumin level and LOS($P = 0.05$). It acts as a predictive marker of the outcome of patients after PD. Both association between age and postoperative albumin level with outcome need to be validated in large volume randomized trials. Another important factor for the success of ERAS protocol in our patients was adequate preoperative optimization and improved surgical technique.

Our study has certain limitations. It is a single center low volume single arm study. A larger multi institutional randomized study with a control arm will be required to

further evaluate and compare the ERAS protocol in patients after PD.

In conclusion, application of ERAS protocol after PD is feasible and decreases the LOS and the risk of postoperative complications.

Contributors

TM proposed the study. TM performed the research. MR and TM wrote the first draft. MR collected and analyzed the data. DVK and SHS edited the manuscript and provided data. All authors contributed to the design and interpretation of the study and to further drafts. TM is the gurantor.

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Ethical approval

The study was approved by the Institute's Ethical Committee of Institute of Medical Sciences, Banaras Hindu University.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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