ORIGINAL ARTICLE

Enhanced recovery pathway in patients undergoing distal pancreatectomy: a case-matched study

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Abstract

Background: Enhanced recovery (ER) pathways have improved outcomes across multiple surgical specialties, but reports concerning their application in distal pancreatectomy (DP) are lacking. The aim of this study was to assess compliance with an ER protocol and its impact on short-term outcomes in patients undergoing DP.

Methods: Prospectively collected data were reviewed. One hundred consecutive patients undergoing DP were treated within an ER pathway comprising 18 care elements. Each patient was matched 1:1 with a patient treated with usual perioperative care. Match criteria were age, BMI, ASA score, lesion site, and type of disease.

Results: Adherence to ER items ranged from 15% for intraoperative restrictive fluids to 100% for intraoperative warming, antibiotic and anti-thrombotic prophylaxis. Patients in ER group experienced earlier recovery of gastrointestinal function (2 vs. 3 days, $p < 0.001$), oral intake (2 vs. 4 days, $p < 0.001$), and suspension of intravenous infusions (3 vs. 5 days, $p < 0.001$). Overall morbidity was similar in the two groups (72% vs. 78%). Length of hospital stay (LOS) was reduced in ER patients without postoperative complications (6.7 ± 1.2 vs. 7.6 ± 1.6 days, $p = 0.041$).

Conclusions: An ER pathway for DP yielded an earlier postoperative recovery and shortened LOS in uneventful patients. Postoperative morbidity and readmissions were similar in both groups.

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Introduction

Despite the introduction of minimally invasive approaches, multidisciplinary patient management and centralization policies, pancreatic surgery still carries a significant risk of postoperative major morbidity and mortality even in high-volume institutions.[1] Moreover, patients undergoing pancreatic resection recover slower than expected, and recent research found that patients treated with pancreatic cancer resection take around 6 months to return to preoperative quality of life.[2]

An enhanced recovery after surgery (ER) pathway is an evidence-based framework designed to provide patients with the best perioperative care.[3] This approach was originally applied to patients undergoing colorectal surgery yielding reduced morbidity, length of hospital stay (LOS), and societal costs to traditional perioperative care.[4,5] Recently, ER protocols have been carried out in multiple surgical areas and promising results have been reported following gastrectomy,[6] hysterectomy,[7] cystectomy,[8] hip replacement,[9] and bariatric surgery.[10]

In recent years, an increasing number of novel perioperative care bundles for patients undergoing pancreaticoduodenectomy have been reported.[11] Most studies showed encouraging results compared to usual perioperative care in terms of shortened LOS, similar postoperative morbidity, and no increase in hospital readmissions and hospital costs.[12] The most significant advantage in recovery seems to be achieved in those patients with higher compliance to the care pathway and who do not experience postoperative morbidity.[13]

Distal pancreatectomy (DP) is less commonly performed than pancreaticoduodenectomy, as cancer of the pancreatic body or tail is usually diagnosed at a more advanced stage than pancreatic head lesions.[14] Conversely, due to the increased detection of asymptomatic precancerous disease on cross-sectional imaging done for other reasons, the proportion of patients undergoing DP is increasing. However, only a few reports deal with the implementation of an ER pathway in DP.[15,16] Therefore the aim of the present study is to assess patient compliance to an ER protocol specifically designed for DP and verify its impact on postoperative outcomes compared to usual perioperative care.

Methods

This study represents a review of a prospectively collected database including patients undergoing distal pancreatectomy between January 2011 and December 2014 within an 18-item ER pathway, which was defined with active contribution from the ER Society®. The pathway was applied in 106 consecutive unselected patients undergoing elective DP for a lesion of the pancreatic body or tail. Six patients who underwent palliative surgery because of intraoperative detection of peritoneal metastases (n = 5), or locally advanced disease (n = 1) were excluded from the study. The remaining 100 patients were included in the study. For each ER patient, a researcher blinded to patients postoperative outcome identified one control matched patient from our Institution database where parameters have been prospectively collected. Match criteria were chosen according to previous studies identifying risk factors for postoperative morbidity and pancreatic fistula following DP.[17,18] The following match criteria were used in this study: age (± 5 years), preoperative physical status as defined by American Society of Anesthesiologists (ASA) score (1–2 or 3–4), BMI grading (<25, 25–30, >30), site of pancreatic lesion (body or tail), and type of disease (benign or malignant). In the event of multiple matching patients, the closest one in time was chosen. The patients identified for the control group underwent DP between January 2007 and December 2010.

Table 1 shows the differences in perioperative care processes between the ER pathway and the previously adopted protocol. Demographics, ASA score, routine blood tests, nutritional status, and primary diagnosis were recorded in all patients before surgery. All patients received antibiotic prophylaxis with cefazolin (2 g) 30 min before surgery, to repeat if surgery lasted more than 4 h. To prevent hypothermia, a blanket warming system (Bair Hugger®, Augustine Medical, Inc.) was used. All operations were performed by four experienced surgeons of the pancreatic surgery unit, who had completed a training program in our high-volume hospital[19] including their learning curve in laparoscopic pancreatectomy.[20] DP with splenectomy and standard lymphadenectomy was performed in all cancer patients. A spleen-preserving procedure was considered as the first option in patients with benign diseases. One drain was routinely placed close to the pancreatic stump. In case of non-sinister fluid in the drain with amylase value less than 3-fold the normal range, removal of the pancreatic surgical drain was suggested.

Operative time, operative blood and fluid losses, and blood transfusions were recorded for each patient. Postoperative fluid infusion, food intake, and mobilization (minutes out of bed) were registered daily until discharge. Thromboembolic disease prophylaxis was performed by nadroparin calcium (0.4 mL), subcutaneously starting 6 h after surgery as per institutional protocol. Postoperative analgesia was ensured by continuous thoracic epidural infusion of 0.2% ropivacaine (4–6 mL/h) or, when contraindicated, by intravenous morphine hydrochloride (patient-controlled administration) at a maximum of 4 mg/h with a single dose of 1 mg and free interval of 10 min. In addition, all patients received opioid-sparing multimodal analgesia including acetaminophen and NSAIDs.

Outcome measures

Our primary outcome measure was primary admission LOS, defined as the number of postoperative nights spent in the hospital. Secondary outcomes included overall postoperative morbidity defined as the number of patients experiencing any complication within 30 days after surgery, early postoperative recovery measures (i.e. return of gastrointestinal function, mobilization, suspension of intravenous fluid infusions), and 30-day hospital readmissions.

According to our previous studies, criteria to identify postoperative complications were *a priori* defined.[21] Microbiological analysis and positive culture proved all infectious complications. Postoperative complications were graded according to Clavien–Dindo classification,[22] which was validated in pancreatic surgery.[23] Complications graded as III to V were considered as major. Pancreatic fistula was defined and graded according to ISGPF criteria.[24] Delayed gastric emptying was defined as need for nasogastric decompression or vomiting occurring after POD 7.[25] Post-pancreatectomy Haemorrhage was defined according to ISGPS definition.[26]

Patients were discharged after meeting the following criteria: no clinical or laboratory evidence of postoperative complications or untreated medical problems, good pain control with oral analgesics, adequate oral food intake and mobilization, recovery of bowel function, and acceptance of discharge by the patient. Hospital readmission for any postoperative complication occurring within 30 days after discharge was recorded.

Statistical analysis

All prospectively collected data were registered in an electronic database. Normality was assessed by inspection of frequency histograms. Descriptive data are reported as mean (standard deviation), median (25th percentile – 75th percentile), or number of patients or percentage. Categorical variables were compared by the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared by the

Table 1 Comparison between the ER pathway and usual care perioperative items

Perioperative process	ER pathway	Usual care
Preoperative counselling	Multidisciplinary counselling	Traditional informed consent
Preoperative bowel preparation	No bowel preparation	Oral bowel preparation with sodium phosphate
Preoperative fasting	Clear fluids until 2 h before surgery	Overnight fasting
Pre-anesthetic medication	No pre-medication	Short-acting sedatives at anesthesiologist's discretion
Anti-thrombotic prophylaxis	LMWH starting 6 h after the end of surgery	LMWH starting 6 h after the end of surgery
Antibiotic prophylaxis	Antibiotic prophylaxis administered 30 min before incision	Antibiotic prophylaxis administered 30 min before incision
Epidural analgesia	Thoracic epidural analgesia started before surgical incision. Stop test and removal on POD 4	Thoracic epidural analgesia started before surgical incision. Stop test and removal on POD 5
Maintenance of normothermia	Intraoperative active warming system	Intraoperative active warming system
Intraoperative fluids	Balanced IV infusions, avoiding fluid overload (<6 mL/kg/hour)	Liberal IV fluid regimen
Nasogastric tube	Removal at the end of surgery	Removal on POD 1 if drainage output $\leq$ 300 mL
PONV prophylaxis	Multimodal prophylaxis: dexamethasone 4 mg after induction of anesthesia; ondansetron 2 h before the end of surgery	At anesthesiologist's discretion
Glycemic control	Continuous IV insulin infusion if needed to prevent hyperglycemia	Continuous IV insulin infusion if needed to prevent hyperglycemia
Oral liquids	At will from POD 1	At surgeon's discretion
Oral solid food	At will from POD 2	At surgeon's discretion
Postoperative fluid infusions[a]	20 mL/kg/on POD 1 15 mL/kg/on POD 2 IV fluid suspension planned on POD3	30 mL/kg/day to continue until adequate oral intake
Postoperative mobilization	Two hours out of bed on POD 1 Four hours out of bed on POD 2 with self-care in bathroom and assisted deambulation	Sit out of bed on POD 1 Two hours out of bed on POD 2 Self-care in bathroom from POD 3
Urinary catheter removal	Within POD 2	After suspension of intravenous fluid infusions
Peripancreatic drain removal	On POD 4 if non-sinister fluid in the drain and drain amylase value less than 3-fold the normal range	At surgeon's discretion, if non-sinister fluid in the drain and drain amylase value less than 3-fold the normal range

ER: enhanced recovery after surgery; IV: intravenous; PONV: postoperative nausea and vomiting, POD: postoperative day.
[a] Hydroelectrolytic balanced solution containing glucose 5.5%, sodium 58 mEq/L, potassium 28 mEq/l, calcium 3.2 mEq/l.

Student's *t* test if normally distributed, or non-parametric Mann–Whitney *U* test. Univariate and stepwise backward elimination multivariate linear (for continuous outcomes) or logistic (for binary outcomes) regression analyses were performed to identify preoperative and intraoperative factors independently associated with LOS and postoperative morbidity. The variable LOS was log-transformed because not-normally distributed.

The significance level was set at 0.05. Data analysis was performed using Stata® version 13.1 (StataCorp LP, College Station, Texas, USA).

Results

No significant difference for demographics and preoperative characteristics was found between ER and usual care patients (Table 2). A significantly higher proportion of patients in the ER group underwent laparoscopic surgery (65 vs. 35, $p < 0.001$), whereas no difference was found between groups in the proportion of patients who completed a splenopancreatectomy versus a spleen-preserving procedure. Mean intravenous fluid infusion rate was 5.3 mL/kg/hour lower in the ER than in the control group ($p = 0.001$).

Table 3 shows the adherence to perioperative items in the ER group. No adverse effect related to specific ER items, including lack of bowel preparation and shortening of preoperative fasting period, and omission of nasogastric drainage was observed. Only 2 patients in the ER group versus 5 patients in the usual care group required nasogastric tube reinsertion during the postoperative course ($p = 0.445$). However, in the ER group, the adherence to intraoperative fluid infusion policy (15%) and specific postoperative pathway items such as mobilization out of bed on POD 1 (33%), removal of urinary drainage (37%) by POD 2, solid food on POD 2 (66%), suspension of intravenous

Table 2 Preoperative and intraoperative variables

	ER (n = 100)	Usual care (n = 100)	p-Value[a]
Age (years)	62.4 (13.4)	60.4 (13.8)	0.300
Gender: Men/Women	49/51	44/56	0.571
ASA score: I-II/III-IV	85/15	84/16	1.000
Diabetes	29	19	0.136
BMI (kg/m^2)	25.1 [22.7–27.7]	24.7 [22.2–28.1]	0.617
Lesion site: body/tail	70/30	66/34	0.649
Lesion size (mm)	28 [19–40]	30 [19–45]	0.631
Serum hemoglobin (g/L)	133 (16)	135 (16)	0.378
Cancer patients	46	39	0.391
Laparoscopy	65	35	<0.001
Conversion to open surgery	12 (18.5%)[b]	10 (28.6%)[b]	0.312
Splenectomy	74	64	0.169
Pancreatic stump closure			
Linear stapler	72	30	<0.001
Hand-sewn	28	70	
Duration of surgery (min)	225 [185–280]	213 [165–260]	0.112
Operative blood loss (mL)	300 [200–550]	375 [200–775]	0.103
Intraoperative transfusion	23	30	0.336
Intraoperative fluid infusions (mL/kg/h)[a]	9.5 (2.7)	14.8 (5.7)	<0.001

ASA: American Society of Anesthesiologists; BMI: body mass index.
Data are mean (standard deviation) or median [25th percentile – 75th percentile], or number of patients.
[a] Refers to maintenance fluid infusions (i.e. crystalloids, colloids) excluding blood products.
[b] Percentage related to laparoscopic resections.

infusions by POD 3 (59%), and suspension of epidural analgesia on POD 4 (63%) was suboptimal. Forty-four patients met criteria for drain removal during hospital stay, and 41 (93%) of them successfully removed it.

Table 4 shows an earlier postoperative recovery in the ER group compared to usual care in terms of recovery gastrointestinal function, need for intravenous fluids and urinary drainage, timing of abdominal drain removal, and amount of time spent out of bed in the first two days after surgery. Although intravenous infusions were stopped earlier in the ER group, no difference was found in the number of patients requiring liquids to be restarted (n = 4 in ER vs. n = 3 in usual care group). A greater number of patients in the ER group removed the peripancreatic drain before discharge compared to usual care (n = 60 vs. n = 42 patients; p = 0.016).

Table 5 reports postoperative outcomes in both groups. No difference in mortality, overall morbidity, and complication

Table 3 Adherence to perioperative care elements for patients in the ER group

	ER (n = 100)
Preoperative	
Preadmission counselling	98
No oral bowel preparation	98
Short preoperative fasting	97
No premedication	100
Intraoperative	
Antibiotic prophylaxis	100
Epidural analgesia	82
PONV prophylaxis	79
Intraoperative warming	100
Intraoperative balanced IV fluids	15
Postoperative	
Anti-thrombotic prophylaxis	100
No NGT	96
Mobilization out of bed (2 h) on POD 1	33
Oral liquids on POD 1	80
Solid food on POD 2	66
Urinary catheter removal out within POD 2	37
IV fluids suspension within POD 3	59
Epidural removal within POD 4	52 (63%)[a]
Abdominal drain removal	41 (93%)[b]

Data are number of patients, otherwise specified.
[a] Refers to 82 patients who received epidural analgesia.
[b] Refers to 44 patients meeting criteria for drain removal.

severity was found. Relaparotomy was needed in 4 patients in the ER group and 3 patients in the usual care group. Causes of reoperation were bowel perforation (n = 2 in ER vs. n = 0 in usual care group), early bleeding within 48 h from surgery (n = 1 in ER vs. n = 1 in usual care group), and late bleeding

Table 4 Postoperative recovery measures

	ER (n = 100)	Usual care (n = 100)	p-Value
First passage of flatus	2 [2–3]	3 [2–4]	<0.001
First passage of stool	5 [4–5]	5 [4–6.5]	<0.001
First solid food intake	2 [2–3]	4 [3–5]	<0.001
Suspension of intravenous fluids	3 [3–4]	5 [4–5]	<0.001
Removal of urinary drainage	3 [2–3]	4 [3–5]	<0.001
Mobilization on POD 1 (minutes)	92 (66)	54 (32)	<0.001
Mobilization on POD 2 (minutes)	159 (70)	109 (67)	<0.001
Transition to oral analgesia	4 [4–5]	4 [4–5]	0.107
Removal of abdominal drainage	5 [5–7]	7 [6–8]	0.004

Data are median postoperative day [25th percentile – 75th percentile] or mean (standard deviation).
POD: postoperative day.

Table 5 Postoperative outcomes

	ER (n = 100)	Usual care (n = 100)	p-Value
30-day overall morbidity	72	78	0.414
Clavien–Dindo complication grade			
0 – no complications	28	22	0.520[b]
I	21	23	
II	40	46	
III – IV	11	9	
V – mortality	0	0	
LOS in all patients			
Mean (SD)	8.7 (3.7)	9 (3.8)	0.180[a]
Median [i.q.r.]	8 [6–9]	8 [7–10]	
LOS in uneventful patients			
Mean (SD)	6.7 (1.2)	7.6 (1.6)	0.041[a]
Median [i.q.r.]	7 [6–7]	7 [6.5–9]	
LOS in patients with complication grade I – II			
Mean (SD)	8.3 (2.6)	8.5 (2.4)	0.497[a]
Median [i.q.r.]	8 [7–9.5]	8 [7–10]	
LOS in patients with complication grade III – V			
Mean (SD)	15.3 (6.7)	17.1 (7.7)	0.652[a]
Median [i.q.r.]	14 [11–18.5]	17 [12–20]	
30-day hospital readmission	12	8	0.480
Pancreatic fistula	56	64	0.312
Grade A	39	53	0.065
Grade B – C	17	11	0.228
Post-pancreatectomy hemorrhage	6	6	1.000
Abdominal fluid collection[c]	6	5	1.000
Delayed gastric emptying	2	1	1.000
Wound infection	5	4	1.000
Cardiorespiratory complications	8	13	0.311
Urinary tract infection	2	5	0.445

Data are number of patients (%), otherwise specified. LOS: length of hospital stay; i.q.r.: interquartile range.
Numbers of single type of complication do not add up to the number of overall complications within the two groups, in relation to the possible occurrence of more types of complication in some patients.
[a] Refers to Mann–Whitney *U* test.
[b] Refers to chi-square test for trend.
[c] Refers to abdominal fluid collection requiring percutaneous or endoscopic drainage.

related to pancreatic fistula (n = 1 in ER vs. n = 2 in usual care group). ER pathway significantly shortened LOS in patients with an uneventful postoperative course. Readmission rates were similar in the two groups. All patients readmitted to the ward had a complication related to pancreatic fistula. Causes of readmission were abdominal fluid collection requiring antibiotic, radiological or endoscopic treatment (n = 9 in ER vs. n = 8 in usual care group), and late bleeding (n = 3 in ER vs. n = 0 in usual care group). No difference was found considering single complications, including pancreatic fistula and cardiorespiratory complications. In cancer patients, the proportion receiving adjuvant chemotherapy after distal pancreatectomy was similar between groups (n = 39, 85% vs. n = 30, 77%; p = 0.412).

Table 6 shows univariate and multivariate linear regression analyses to identify factors associated with LOS. Older age (70+ years) and intraoperative blood loss greater than 500 mL were the only factors independently associated with prolonged LOS, while the laparoscopic approach and the ER pathway did not have a significant impact on LOS. Similar results were found when logistic regression analysis were performed for postoperative morbidity (data not shown).

In the ER group, a subgroup analysis on pathway compliance stratifying patients by postoperative complication severity and occurrence of pancreatic fistula was carried out. Overall, a higher adherence was found for patients who did not experience postoperative complications (Supplementary material 1). Specifically, adherence to solid food intake on POD 2 was significantly higher in patients with an uneventful course, while a progressively lower compliance was found in accordance with the severity of postoperative complications. In addition, patients developing a clinically significant (ISGPF grade B – C) pancreatic fistula were significantly less likely to adhere to early mobilization milestones, suspension of intravenous fluid infusions by POD 3, and removal of epidural catheter by POD 4 (Fig. 1).

Discussion

The present study, comparing perioperative outcomes in 100 patients treated within an ER pathway for DP with 100 usual care matched controls, found that ER improves short-term recovery, and reduces length of hospital stay in patients with an uneventful postoperative course, whereas postoperative morbidity and post-discharge readmissions were similar between groups. Moreover, our analysis showed that adherence to early postoperative ER items was lower in patients who developed postoperative complications, in particular clinically relevant pancreatic fistula.

ER pathways are evidence-based, multimodal, and multidisciplinary perioperative programs aiming to reduce surgical stress and to improve patient recovery and quality of life after surgery.[3] Through a preoperative education session, ER engages patients in their own recovery providing key information on their recovery milestones and expectations. It is also intended to reduce unwanted variability in patient management, providing a structured timeline for the healthcare personnel. A recent meta-analysis of 38 randomized trials across multiple specialties including colorectal, foregut, genitourinary, thoracic and joint surgery concluded that ER pathways reduced morbidity risk by about 30% and were associated with reduced LOS by about 1 day overall.[28]

Table 6 Univariate and multivariate linear regression to determine factors associated with postoperative length of stay

	Univariate analysis			Multivariate analysis		
Variable	**Beta[a]**	**95% C.I.**	**p-Value**	**Beta[a]**	**95% C.I.**	**p-Value**
Older age (70+ years)	0.113	0.02–0.21	0.018	0.115	0.02–0.21	0.015
Male gender	0.009	−0.08–0.10	0.848			
ASA score 3+	0.064	−0.07–0.19	0.334			
Obese (BMI $\geq$ 30 kg/m^2)	0.073	−0.07–0.22	0.318			
Cancer	0.085	−0.01–0.18	0.074			
Laparoscopy	−0.027	−0.12–0.07	0.566			
Stapler for pancreatic stump closure	−0.081	−0.17–0.01	0.077			
Intraoperative blood loss > 500 mL	0.112	0.02–0.21	0.020	0.114	0.02–0.21	0.018
IV fluid infusion < 6 mL/kg/hr	−0.012	−0.13–0.11	0.838			
ER pathway	−0.043	−0.14–0.05	0.363			

ASA, American Society of Anesthesiologists; BMI, body mass index; IV, intravenous.
[a] Should be interpreted as percentage of change in LOS.

DP is major surgical procedure where serious complications occur in around 10% of patients, significantly lower than a Whipple procedure. However, around half of patients develop pancreatic fistula, which is clinically relevant (i.e. ISGPF grade B–C) in 10–20 percent of patients.[27] Risk factors for postoperative morbidity including preoperative physical status, obesity, high intraoperative blood loss and morphology of the pancreatic remnant have been inconsistently reported in the past, and reliable scores to predict complications after DP are missing.[17,18,29] In this setting, where morbidity is dominated by a surgical complication, the impact of ER pathways on clinical outcomes may differ from other surgical fields such as colorectal surgery where ER significantly reduces postoperative medical complications.[5] When compared to traditional care pathways, protocols incorporating ER items were associated with a shorter LOS in patients undergoing pancreaticoduodenectomy, although both postoperative mortality and major morbidity rates were similar.[11] Only a couple of small-sized studies reported on the implementation of an enhanced recovery program showing improved postoperative recovery following laparoscopic DP.[15,16]

In our series, the implementation of an extensive ER pathway incorporating 18 evidence-based perioperative interventions was not associated with any harmful effect. Shortening preoperative fasting period was not associated to any episode of pulmonary aspiration at time of anesthesia induction. Furthermore, nasogastric tube removal at the end of surgery did not increase episodes of nausea and vomit nor its reinsertion rate compared to usual care. Adherence to ER elements was high for preoperative

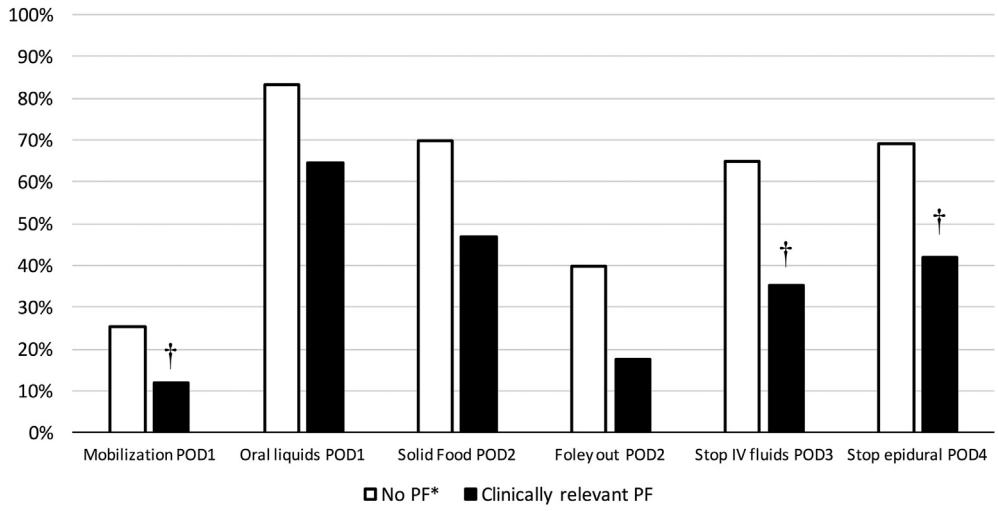

Figure 1 Adherence to postoperative ER items according to occurrence of clinically relevant pancreatic fistula. POD: postoperative day, PF: pancreatic fistula. * Includes patients with no pancreatic fistula and ISGPF grade A pancreatic fistula. † $p < 0.05$

and intraoperative elements with the exception of restrictive intravenous fluid infusion. During surgery, patients of the ER group received significantly less intravenous fluids than controls, in which a liberal fluid policy was applied. However, mainly due to hypovolemia-related hypotension, the adherence to the target infusion regimen was poor and most ER patients required more intravenous maintenance fluids than planned. It is still unclear how to define a restrictive fluid regimen in pancreatic surgery, as current knowledge is mostly translated from experiences in other surgical areas. In colorectal surgery, Brandstrup *et al.* observed that an excess fluid administration leads to weight gain of more than 2.5 kg on the day of surgery, and was proportionally associated with an overall increase of complications.[30] Tailoring fluid therapy based on more objective measures of intravascular volume, commonly called goal-directed fluid therapy (GDFT), could avoid both splanchnic hypoperfusion due to a restrictive fluid policy and prevent fluid overload, promoting gastrointestinal function recovery,[31] and reducing postoperative morbidity rate and hospitalization[32,33] especially in high-risk patients.[34,35]

In the present cohort, adherence to postoperative ER elements was suboptimal confirming results from previous colorectal surgery series where adherence was consistently lower for postoperative care processes.[36–38] In our study, only one third of patients met mobilization milestones on the first day after surgery and urinary drainage persisted beyond POD 2 in around 60% patients. Moreover, more than one third of ER patients did not receive solids as scheduled, and intravenous infusions were prolonged after POD 3. Nonetheless, patients in the ER group reached short-term recovery milestones such as tolerance of oral intake with suspension of fluid infusions, return of gastrointestinal function, and ability to mobilize out of bed significantly earlier than the usual care group. Adherence to postoperative elements may be difficult to interpret as it is confounded by the patient's recovery status.[39] For example, patients developing a pancreatic fistula may experience early gastrointestinal symptoms delaying the return to oral intake and leading to prolonged bed rest and intravenous infusions. In fact, early low compliance to postoperative ER interventions, particularly solid food intake, was often associated to the occurrence of postoperative complications and clinically relevant pancreatic fistula, confirming previously reported outcomes following pancreaticoduodenectomy.[13] Therefore, flagging patients with low compliance to early postoperative ER elements may allow identifying a subgroup of patients necessitating extra care, or requiring further clinical examination (e.g. diagnostic imaging).

Overall morbidity was rather high in both groups. This is probably related to the rigorous adoption of complication definitions from previous consensus, and because of the dominant role of pancreatic fistula, which makes up for more than half of the experienced morbidity but is not clinically relevant in most patients. Differently from other surgical specialties,[28] ER pathway did not reduce overall morbidity following DP compared to usual care, whereas hospital stay was reduced only in patients who did not experience postoperative complications. In a previous small-sized retrospective unmatched study where only laparoscopic DPs were included, ER reduced LOS by 3 days compared to usual care.[15] However, in our study the differences in perioperative management were not as pronounced as in the former study. In fact, the usual care protocol in our institution already included several enhanced recovery items such as intraoperative warming, epidural analgesia, early removal of nasogastric tube, and early mobilization. It should also be noted, that the proportion of patients treated with laparoscopy was significantly higher in the ER group. In this group, the use of a stapling device to suture the pancreatic stump was also predominant. Nonetheless, multivariate analyses found that both laparoscopy and the use of a stapler were not significantly associated with shorter LOS or fewer complication, confirming results from a previous study comparing outcomes for patients undergoing laparoscopic versus open DP in our institution.[40] Additionally, our findings may have been influenced by the relevant conversion rate in this series, which may neutralize the recovery benefits associated with laparoscopic surgery. In the context of colorectal surgery, ER pathways have shown to significantly reduce the gap in postoperative outcomes between patients undergoing laparoscopic or open resection, and this may be the case.[41] This finding would require confirmation in a randomized controlled trial of patients undergoing laparoscopic versus open DP treated within an enhanced recovery program.

Strengths and limitations

Although data was prospectively collected in our institutional electronic database, our analysis carries intrinsic limitations of all observational studies. To minimize the risk of bias, a consecutive unselected series of patients undergoing DP in our institution was matched to a control group carrying a surgical risk as close as possible to the ER group. Although there is no consensus on intraoperative risk factors (e.g. pancreatic stump characteristics, estimated blood loss), match criteria included previously identified preoperative factors associated with morbidity after DP such as age, body mass index, and ASA physical status score. Another limitation of this study may be considered the use of LOS as measure of postoperative recovery, as it may be influenced by many organizational, non-clinical factors such as the healthcare system in which the study is carried out.[42] As a matter of fact, in our series around half of the patients come from distant Italian locations, thus it is not uncommon to keep a patient hospitalized for an extra day or two despite meeting all criteria for discharge. Alternatively, a valid measure of short-term postoperative recovery may be the time to readiness for discharge (i.e. postoperative days to achieve specific discharge criteria),[43] but this variable was originally not included in the institutional registry and it could not be reliably collected in retrospective fashion for both groups.

Main strengths of this study were that it followed recent recommendations for reporting of trials on enhanced recovery,[44] and

provided definitions of adherence and standardized outcome measures. So far, most of the available comparative studies fail to describe the individual differences in perioperative care elements between usual care and ER, and omit adherence definitions for each implemented intervention. In addition, this study was carried out in a high-volume center for pancreatic surgery with extensive experience in perioperative care and enhanced recovery, limiting the potential confounding effect of an implementation phase.

Conclusions

In conclusion, an ER pathway for DP yielded an earlier postoperative recovery and shortened length of hospital stay in patients who did not experience complications. Postoperative morbidity and post-discharge readmissions were similar between groups. Adherence to the pathway was higher for preoperative and intraoperative elements, but it was suboptimal for postoperative interventions. Since low compliance to early postoperative ER elements is often associated to complications, especially clinically relevant pancreatic fistula, such patients should be carefully managed.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2016.10.014