ORIGINAL ARTICLE

Evaluation of an enhanced recovery protocol after pancreaticoduodenectomy in elderly patients

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Abstract

Background: Recent evidence has shown that enhanced recovery after surgery (ERAS) protocols decrease hospital stay following pancreaticoduodenectomy (PD). The aims of this study were to assess the feasibility and to evaluate the effect of introducing ERAS principles after PD in elderly patients.

Methods: Patients ≥75 years were defined as elderly. Comparison of postoperative outcome was performed between 22 elderly patients who underwent ERAS (elderly ERAS + patients) and a historical cohort of 66 elderly patients who underwent standard protocols (elderly ERAS-patients).

Results: The lowest adherence with ERAS among elderly patients was observed for starting a solid food diet within POD 4 (n = 7) and early drains removal (n = 2). The highest adherence was observed for post-operative glycemic control (n = 21), epidural analgesia (n = 21), mobilization (n = 20) and naso-gastric removal in POD 0 (n = 20). Post-operative outcomes did not differ between elderly ERAS+ and elderly ERAS- patients. In patients with an uneventful postoperative course, the median intention to discharge was earlier in elderly ERAS + patients as compared to the elderly ERAS- patients (4 days versus 8 days, $P < 0.001$).

Conclusion: An ERAS protocol following PD seems to be feasible and safe among elderly although it is not associated with improved postoperative outcomes.

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Introduction

By the end of the 1990s some Authors proposed an optimized management of perioperative care for elective surgical patients.[1,2] This enhanced recovery after surgery (ERAS) program includes a multimodal rehabilitation approach that accelerates recovery decreasing post-operative morbidity and hospital stay after surgical procedures.[3–5] ERAS or fast-track surgery methods include minimally invasive techniques, optimal pain control, and aggressive postoperative rehabilitation, including early enteral (oral) nutrition and ambulation.[6] The benefits of introducing ERAS programs have been consistently demonstrated, particularly in colorectal cancer.[7–9] Several studies have demonstrated that ERAS is effective in reducing length of hospital stay and overall complications rate across different surgical specialties.[10,11] Despite mounting evidence for improved outcomes for other surgical procedures, many pancreatic surgeons have remained skeptical that such results can be achieved following pancreaticoduodenectomy (PD). Nevertheless some studies have recently demonstrated that an ERAS protocol is safe and feasible for pancreatic surgery.[12] Only one study[13] has investigated the feasibility of this approach in elderly patients. Although there are no studies that suggest that age should be a criterion for exclusion from ERAS protocols, older patients' attitudes to ERAS may represent a barrier to the implementation of such a protocol.[14] The aims of this study were i) to assess the compliance to an ERAS protocol following PD in elderly patients and ii) to evaluate the effect on postoperative outcomes after introducing ERAS in this population.

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Methods

Study population

This was a retrospective, observational study. Given the retrospective nature of the study, ethical committee approval was waived. Since January 2013 an ERAS protocol was introduced at the Department of Surgery of Ancona University. Overall, 102 consecutive patients agreed to participate in the ERAS protocol following PD and signed an informed consent. Of those, 22 (21%) patients were ≥75 years of age and were defined as the elderly group. The remaining 80 patients <75 years represented the control group in the assessment of ERAS compliance.

Perioperative management and assessment of ERAS compliance

The ERAS protocol was inspired by the recommendations proposed by the ERAS society.[15] Table 1 shows differences between previously adopted perioperative care protocol and the ERAS pathway. Several items differed from those proposed by the ERAS society.[15] In particular, i) preoperative biliary drainage was always carried out in the presence of jaundice with conjugated bilirubin >5 mg/dL, ii) carbohydrate supplementation drinks were avoided, and iii) oral laxatives were not routinely used. A pylorus-preserving PD with standard lymphadenectomy was the preferred operation. The reconstruction phase included an end-to-side duct-to-mucosa pancreatico-jejunostomy. Fluid balance was monitored using the FloTrac® sensor (Edwards Lifesciences LLC, One Edwards Way-Irvine, CA, USA).

Evaluation of ERAS efficacy in elderly patients

A 3:1 case-matched study design was used. Comparisons were performed between 22 elderly patients who underwent ERAS protocol (Elderly ERAS + patients) and a matched group of 66 elderly patients who underwent previously adopted protocol before the implementation of the ERAS program (Elderly ERAS-patients). All these 66 patients were operated by the same surgical team at another institution (Ospedale "Sacro Cuore-Don Calabria") between 2009 and 2012. Patients were matched 1:3 by age, Body Mass Index (BMI), American Society of Anesthesiology (ASA) score, and Fistula Risk Score (FRS). Complications were defined and classified according to Dindo *et al.*[16] Pancreatic fistula (PF) was defined according to the International Study Group of Pancreatic Fistula (ISGPF) as any

Table 1 Main differences between previously adopted perioperative care protocol and ERAS items following pancreatico-duodenectomy (PD)

Item	Standard protocol	ERAS pathway
Preoperative counseling	At surgeon's discretion	Yes
Preoperative biliary drainage	Yes	Yes
Preoperative nutrition	No	No
Bowel preparation	At surgeon's discretion	No
Pre-anesthetic medication	No	No
Anti-thrombotic prophylaxis	Yes	Yes
Antimicrobial prophylaxis	Yes (30–60 min before incision)	Yes (30–60 min before incision)
Epidural analgesia	At anesthetist's discretion and/or if not contraindicated	Yes (mid-thoracic)
Stop of analgesia	At anesthetist's discretion	Within POD3
Intravenous analgesia	At anesthetist's discretion and/or if epidural analgesia contraindicated	No
Incision	Midline laparotomy	Midline laparotomy
Avoiding hypothermia	Always	Always
Postoperative glycemic control	Subcutaneous or intravenous insulin at anesthetist discretion	Intravenous insulin
Nasogastric intubation	At surgeon's discretion	POD0 removal
Fluid balance	At anesthetist's discretion	Near-zero balance, balanced crystalloids
Perianastomotic drains removal	At surgeon's discretion	Within POD3 if AVD < 2000 U/l in POD1
Somatostatin analogs	At surgeon's discretion	No
Urinary drainage	Transurethral catheterization for 2–3 days	Urinary catheter removal within POD3
Postoperative nutrition	At surgeon's discretion	Liquid and soft diet in POD1-2, solid food within POD4
I.V. fluid withdrawal	At surgeon's discretion	Within POD4
Early mobilization	Always in POD1	Always in POD1

POD, Postoperative day; AVD, Amylase value in drains.

measurable volume of fluid on or after postoperative day 3 with amylase content greater than 3 times the serum amylase activity.[17] Delayed gastric emptying was defined as need for naso-gastric decompression or vomiting occurring after postoperative day 10.[18] Fistula risk was determined using the validated, 10-point FRS.[19] Individual FRS scores were calculated and then assigned to 4 risk zones according to Callery and colleagues:[19] negligible risk, low risk, moderate risk, and high risk. These risk zones were then dichotomized into negligible/low and moderate/high risk groups. The length of stay (LOS) of a patient was counted as the date of discharge minus the date of surgery. Days after readmission were not included in the LOS. Patient was deemed ready for discharge (intention to discharge) under all the following criteria: i) patient had to tolerate at least 2 solid meal without nausea and vomiting, ii) patients had to pass flatus or a bowel movement, iii) patient had to be able to rest or mobilize without significant pain taking oral nonopioid analgesics, iv) patient had to be able to sit up, walk, and performs activities of daily living, v) oral temperature, pulse, blood pressure, respiratory rate, and serum hemoglobin had to be normal or consistent with preoperative levels. Post-operative mortality was defined as 30-day and/or in-hospital mortality.

Table 2 Compliance with preoperative, intraoperative and postoperative ERAS items

	All patients (n = 102)	<75 years (n = 80)	≥75 years (n = 22)	P
Intra-operative glycemic control				
No	6 (6%)	5 (6%)	1	0.763
Yes	96 (96%)	75 (94%)	21	
Intra-operative fluid balance (l)[a]	0.5 (–1.6 to 2.5)	0.5 (–1.6 to 2.0)	0.5 (–0.4 to 2.5)	0.163
Intra-operative + POD0 fluid balance (l)[a]	–0.5 (–5.9 to 2.1)	–0.1 (–5.9 to 2.1)	0.4 (–1.7 to 2.1)	***0.043***
Intra-operative + POD0 + POD1 fluid balance (l)[a]	–1.5 (–10.9 to 2.5)	–1.5 (–10.9 to 2.5)	–1.1(–3.4 to 1.1)	0.240
Epidural analgesia				
No	10 (10%)	9 (11%)	1	0.349
Yes	92 (90%)	71 (89%)	21	
Stop of analgesia				
≤POD3	83 (81%)	67 (84%)	16	0.240
>POD3	19 (19%)	13 (16%)	6	
Mobilization				
=POD1	98 (96%)	2 (2%)	2	0.158
>POD1	4 (4%)	78 (98%)	20	
Naso-gastric tube removal				
=POD0	93 (91%)	73 (90%)	20	0.960
>POD0	9 (9%)	7 (10%)	2	
Urinary catheter removal				
≤POD3	79 (77%)	63 (79%)	16	0.549
>POD3	23 (23%)	17 (21%)	6	
Oral liquids				
=POD1	88 (86%)	71 (89%)	17	0.166
>POD1	14 (14%)	9 (11%)	5	
Solid food				
≤POD4	40 (39%)	33 (41%)	7	0.422
>POD4	62 (61%)	47 (59%)	15	
I.V. fluid withdrawal				
≤POD4	78 (76%)	63 (79%)	15	0.301
>POD4	24 (24%)	17 (21%)	7	
Drains removal if POD1 AVD ≤ 2000 U/l				
≤POD3	9 (28%)	7 (39%)	2	0.876
>POD3	24 (72%)	11 (61%)	13	

POD, Post-operative day; AVD, Amylase value in drains.
Values in bold indicate $P < 0.05$.
[a] Values are median (range).

Statistical analysis

Distribution of continuous variables is reported as median and range. Categorical variables are presented as numbers and percentages. The comparison between subgroups was carried out using Mann–Whitney U test for continuous variables. Qualitative data were compared by the Chi square test or Fischer exact test when necessary. All tests were 2-sided. Statistical analyses were performed in SPSS 16.0 for Windows software (SPSS Inc, Chicago, Illinois, USA). P values were considered significant when less than or equal to 0.05.

Results

Compliance with ERAS items in elderly patients undergoing PD

In the group of patients ≥75 years old there were only 4 octogenarians. Table 2 shows compliance with ERAS items by age after the implementation of ERAS protocol. ERAS items adherence was evaluated also comparing elderly patients with negligible/low FRS (n = 7) and those with moderate/high FRS (n = 15). Patients with negligible/low FRS were more likely to have epidural catheterization (7/7 versus 12/15, P = 0.023).

Effect on postoperative outcomes of ERAS undergoing PD in elderly patients

Table 3 shows a comparison between elderly matched ERAS- patients and elderly ERAS + patients for demographics and clinical characteristics. A comparison of operative details and postoperative outcomes is depicted in Table 4. When considering only patients who had an uneventful course, the median LOS was similar for both elderly ERAS- (8 days [7–14 days]) and ERAS + groups (8 days [7–8 days]) (P = 1.000). In patients with an uneventful postoperative course, the median intention to discharge was 8 days among elderly patients ERAS- (6–12 days) whereas it was 4 days (4–6 days) for elderly patients ERAS + (P < 0.001). Overall, only 2 of the 20 patients in the elderly ERAS + group who were discharged alive were discharged to a rehabilitation facility. The remaining patients were discharged home.

Table 3 Comparison of elderly ERAS- patients and elderly ERAS + patients for clinical characteristics

Variable	Elderly ERAS-(n = 66)	Elderly ERAS + (n = 22)	P
Age (years)[a]	77.5 (75–82)	77 (75–82)	1
Gender			
Male	33 (50%)	14	0.267
BMI (Kg/m^2)	25 (18–32)	25 (21–31)	0.981
ASA			
I	5 (34%)	2	0.926
II	42 (64%)	13	
III	1 (2%)	7	
FRS			
Negligible/low	20 (30%)	7	0.894
Moderate/High	46 (70%)	15	

BMI, Body Mass Index; ASA, American Society of Anesthesiology; FRS, Fistula Risk Score according to Callery *et al.*[19]
[a] Values are median (range).

Table 4 Comparison of elderly ERAS- patients and elderly ERAS + patients for operative details and postoperative outcomes

Variable	Elderly ERAS-(n = 66)	Elderly ERAS + (n = 22)	P
Operative time (minutes)[a]	360 (240–600)	325 (240–420)	0.251
Complications			
No	29	6	0.167
Yes	37	16	
Complications grade[b]			
Grade 0	23 (35%)	5	0.212
Grade I–II	26 (39%)	7	
Grade III–IV	16 (24%)	9	
Grade V	1 (2%)	1	
Pancreatic fistula			
No	45 (68%)	18	0.219
Grade A/B/C	21 (32%)	4	
Biliary fistula			
No	57 (86%)	16	0.092
Yes	9 (14%)	6	
Chylous leak			
No	57 (86%)	22	0.158
Yes	9 (14%)	0	
DGE syndrome			
No	55 (83%)	15	0.127
Grade A/B/C	11 (17%)	7	
LOS[a] (days)	11 (3–67)	14 (7–53)	0.253
Intention to discharge (days)[a]	10 (7; 67)	13 (4–45)	0.287
Readmission			
No	55 (83%)	19	0.736
Yes	11 (17%)	3	
Re-exploration			
No	63 (95%)	21	1
Yes	3 (5%)	1	

POD, Post-operative day; LOS, Length of stay; DGE, Delayed gastric emptying.
[a] Values are median (range).
[b] according to Dindo *et al.*[16]

Discussion

PD is a challenging operation with a high rate of complications and a measurable mortality risk even in expert hands.[20] Age

alone is not an absolute contraindication for PD. However an analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data demonstrated that in patients with loco-regional pancreatic cancer, the likelihood of being evaluated by a surgeon decreased 8% with each increasing year of age.[21] Indeed, in the vast majority of the studies the reported morbidity and mortality rates are higher in the group of patients defined as "elderly".[21] However, when considering experiences from single, high-volume, institutions, age is not a predictor of perioperative morbidity and mortality following PD.[22,23] Despite this, a longer length of hospital stay is a typical feature of post-operative recovery after pancreatic resection in older patients and the number of patients requiring ongoing inpatient nursing care at discharge increases significantly with age.[13] Increasing age may therefore represent a limitation to the implementation of an enhanced recovery program after PD. There have been no randomized clinical trials of ERAS protocols after pancreatic surgery, however in the studies performed[12] it seems safe, feasible and associated with a shorter length of hospital stay.[12] The median age reported in these studies was generally under 65 years[12] and specific reports on the feasibility and safety of ERAS approach in elderly patients are lacking. Recently, Coolsen and coworkers[13] addressed this issue comparing 55 patients $\geq$70 years old with other 55 patients $\leq$65 years old. The authors demonstrated that an ERAS program for elderly patients undergoing PD is feasible and safe. In particular, the two groups had similar rates of postoperative complications, mortality, re-laparotomy, and readmission.[13] In the present study, more than half of elderly patients fully adhered to all ERAS items. The only items that were associated with a poor compliance were starting a solid diet within POD4 and an early removal of abdominal drains. The main parameter for the management of abdominal drains was a POD1 AVD <2000 U/I but in many patients the characteristic of the drains fluid as well as logistic issues (i.e. unavailability of laboratory for AVD analysis on Sunday) influenced the surgeons decision. Coolsen *et al.*[13] observed a comparable compliance with ERAS items. For better understating the role of age as a possible barrier for the implementation of ERAS protocol, a comparison with younger patients was also made. Of note, no differences were found in terms of ERAS adherence between young and elderly patients. If the implementation of an ERAS protocol following PD seems achievable in elderly patients, the effects on postoperative outcomes are rather dismal. The implementation of an ERAS protocol was not associated with a lower complication rate and the overall LOS was similar to that observed in those patients treated with a standard perioperative protocol. The relatively short postoperative stay in the control group could explain the lack of a clear benefit of the ERAS protocol as regard this aspect. Probably, the real advantage after the implementation of the ERAS protocol is related to a shorter length of stay in those patients who had an uneventful postoperative course. In the present experience, a significant difference was noted in terms of intention to discharge among elderly patients who had a regular post-operative course yet it did not translate to an actual reduction in LOS. Such differences between the intention to discharge and the real LOS are likely multifactorial including the peculiar modality of reimbursement provided by the Italian Health Service, the high number of patients who live far from the hospital, and the fear of patients to leave early the hospital. The authors recognize that the present study has several limitations. The retrospective design is the major limitation of the present study. However, randomized controlled trials are difficult to organize for multi-modal recovery programs especially because several protocol elements of an ERAS program already have become standard practice in many hospitals during the last decade. Moreover, the sample size, especially for the elderly population, is too small to exclude a type II error.

In summary, an ERAS protocol for PD seems to be feasible in elderly patients and age alone does not represent a barrier for the compliance with ERAS items. An ERAS protocol following PD seems to be safe among elderly although it is not associated with an improved postoperative course.

Conflict of interest

None declared.

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