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ORIGINAL ARTICLE

Influence of Clinical pathways on treatment and outcome quality for patients undergoing pancreatoduodenectomy? A retrospective cohort study

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Summary *Background:* Pancreatic surgery demands complex multidisciplinary management. Clinical pathways (CPs) are a tool to facilitate this task, but evidence for their utility in pancreatic surgery is scarce. This study evaluated the effect of CPs on quality of care for pancreatoduodenectomy.
Methods: Data of all consecutive patients who underwent pancreatoduodenectomy before (n = 147) or after (n = 148) CP introduction were evaluated regarding catheter and drain management, postoperative mobilization, pancreatic enzyme substitution, resumption of diet and length of stay. Outcome quality was assessed using glycaemia management, morbidity, mortality, reoperation and readmission rates.
Results: Catheters and abdominal drainages were removed significantly earlier in patients treated with CP ($p < 0.0001$). First intake of liquids, nutritional supplement and solids was significantly earlier in the CP group ($p < 0.0001$). Exocrine insufficiency was significantly less common after CP implementation (47.3% vs. 69.7%, $p < 0.0001$). The number of patients

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receiving intraoperative transfusion dropped significantly after CP implementation ($p = 0.0005$) and transfusion rate was more frequent in the pre-CP group ($p = 0.05$). The median number of days with maximum pain level >3 was significantly higher in the CP group ($p < 0.0001$). There was no significant difference in mortality, morbidity, reoperation and readmission rates.

Conclusions: Following implementation of a CP for pancreatoduodenectomy, several indicators of process and outcome quality improved, while others such as mortality and reoperation rates remained unchanged. CPs are a promising tool to improve quality of care in pancreatic surgery.

1. Introduction

Pancreatoduodenectomy demands complex and multidisciplinary perioperative management, to mitigate the risk of potentially dangerous postoperative complications. Impaired exocrine and endocrine function after pancreatic resection can lead to malnutrition because of lipid malabsorption and diabetes mellitus. Regardless of improvements in surgical technique and perioperative management, mortality and morbidity after pancreas surgery are relevant issues.[1–3] One reason is that more and more elderly and multimorbid patients are resected.[4]

A possible approach to ensure high quality of perioperative management, is the implementation of clinical pathways (CPs).[5] CPs are intended to advance quality of processes and, consequently, of outcome. They are a timeline protocol for all tasks that have to be performed in the course of a given treatment.[6–8] CPs usually involve all different disciplines that are part of the treatment team and aim to translate evidence into clinical practice.[9,10] CPs have shown favorable perioperative results for a number of operations in gastrointestinal surgery.[11] In the last decade, results of treatment with CPs for patients undergoing pancreatoduodenectomy have been reported.[12–15] The studies showed a reduction in length of stay. Kennedy et al additionally reported a non-significant decrease of complication rates.[12] However, these studies were all but one conducted in Anglo-Saxon countries and only reported selected outcomes.[16] Because the effect of CPs is specific to the health system in which they are implemented, we conducted a study assessing all effects of a CP for pancreatoduodenectomy on process and outcome quality in a German tertiary care hospital.

2. Methods

2.1. CP design, implementation, and content

Since 2006, the Department of Surgery of the Universitätsmedizin Mannheim has performed a stepwise implementation of CPs for different surgical procedures.[17–25] In February 2011, three CPs were introduced for pancreatic surgery: one for pancreaticoduodenectomy, one for distal pancreatectomy, and one for total pancreatectomy. The two last mentioned CPs have been assessed in a separate study.

The content of the pancreatic surgery CPs is based on CPs for fast-track colorectal and bariatric surgery which had been previously established.[18,19] Specific treatment steps were modified to adapt this CP for use in pancreatic surgery. Both the original colorectal CP and the pancreatic surgery CPs are based on national and international treatment and nursing recommendations, as well as on best available evidence. The design and implementation process were carried out by an interdisciplinary (surgery, anesthesiology, physiotherapy, nutritional services) and multihierarchical team.

A first draft of the CP was elaborated after a literature review to identify evidence on perioperative treatment elements. In a second step, pre-existent institutional standards were integrated into the CP. In a last step, a consensus meeting with all project participants was held to agree on a final CP version. Prior to definite implementation, all staff members were trained to work with the CP. After implementation, continuous efforts were made to further develop and improve the CP based on suggestions of staff members.

A full version of the CP is shown in the online appendix. Its main elements include the following items. Hospital admission is scheduled for the day before surgery. Epidural catheter placement is stipulated for all patients. A stepwise oral analgesia scheme, with a basis medication of non-opioids and on demand medication of potent opioids, is included in the CP. Patients are monitored postoperatively in a surgical intermediate care unit for at least one night or in an intensive care unit, if considered necessary by the surgeon and/or anesthesiologist. All patients are encouraged to drink sweetened tea until two hours prior to planned intubation. Pancreas enzymes in the drainage fluid are determined on days three and five, and drains were then removed if respective levels were not elevated. Detailed instructions on how to use an incentive spirometer are given to all patients. Pancreatic enzymes are orally substituted in case of steatorrhea. Glycemia levels are closely monitored. An on-demand insulin scheme is included. The designated time of discharge is postoperative day twelve. Outpatient follow-up appointments are scheduled within 14 days of discharge. Patients are instructed to present at our emergency room in case of clinical abnormalities.

The CP was designed as four-page paper-based document containing all stipulated treatment steps, for the single pre- and postoperative days. They were kept with patients' treatment charts and thus always available for all staff involved in treatment.

2.2. Study design

The study was designed as a single center retrospective cohort study. A research protocol has been developed before beginning the evaluation. The protocol has not been published previously. All patients undergoing elective pancreas head resection, either pylorus-preserving pancreatoduodenectomy (PPPD) or Whipple-Kausch pancreatoduodenectomy, were included according to the "intention-to-treat" principle. The intervention group (CP group) comprised all consecutive patients operated following the implementation of the CP in February 2011 until February 2016. The control group (pre-CP group) comprised consecutive patients operated before CP implementation (July 2006—January 2011). In this retrospective study, there was no formal sample size calculation. Study group sizes were determined in order to obtain equally large groups before and after CP implementation. All data were retrieved by retrospective chart review.

Patients in the CP group were treated according to the CP, whereas the pre-CP group was treated according to the individual judgment of and decisions taken by the treating surgeons. Although several semiformal standards for selected elements of care (e.g. epidural analgesia, early removal of catheters, early mobilization) had been in place, at that time there was no instrument covering the whole treatment continuum.

The study was approved by the competent ethical committee of the Medical Faculty Mannheim of the University of Heidelberg (2015-863R-MA). The study has been registered at the German Clinical Trials Register (DRKS 00016749).

Research is being reported in line with the STROCSS statement (http://www.strocssguideline.com).

2.3. Patient characteristics

Demographic and clinical characteristics included age, sex, preoperative status of patients using the American Society of Anesthesiologists (ASA) physical status classification,[26] body mass index (body weight divided by the square of the height), underlying disease, hemoglobin and serum albumin levels upon preoperative admission.

2.4. Surgery

In both groups (before and after CP implementation), surgery was performed by HPB surgeons with an experience of more than four years. Nine HPB-surgeons performed pancreatic head resections before CP implementation and ten afterwards. Three (18.8%) of them performed surgery in both groups and 13 (81.3%) in only one group. The three surgeons performed 87.1% of the resections before and 44.6% after CP implementation, whereby in more than 75% of cases, one of the three, was part of the supervising surgeons. All surgeons performed the operations according to the in-house standard. Pylorus-preserving pancreatoduodenectomy (PPPD) and classic Whipple-Kausch operation were performed as described previously with a single jejunal loop.[27] Pancreaticojejunostomy and pancreatogastrostomy were achieved in an end-to-side ''dunking'' technique using 2 rows of suturing with absorbable material. Hepaticojejunostomy was performed using a 1-row and all-layer interrupted suture with absorbable monofilament material (5-0 to 6-0). Stents were not used during pancreaticojejunostomy or pancreatogastrostomy. In cases with portal vein involvement, a venous resection was performed to achieve R0-resection. In pancreatic cancer, standard lymphadenectomy was routinely performed.

2.5. Study outcomes

The study evaluated parameters of both process and outcome quality. Process quality was defined as the adherence to treatment specifications as detailed in the CP and was assessed by the following parameters: placement of central venous line and epidural catheter, day of removal of foley catheter and epidural catheter, day of first and second measurement of pancreas enzymes in the drainage fluid, substitution of pancreas enzymes and administration of somatostatin as recommended in the CP, day of removal of intraabdominal drainages and nasogastric tube, application of perioperative single shot antibiotics, postoperative mobilization and day of resumption of liquid and solid diet.

Outcome quality was measured through the following variables: morbidity, mortality, reoperation, length of stay stratified by the presence or absence of complications, pain levels on a numeric rating scale, day of first postoperative defecation and readmission. Morbidity was assessed according to the Clavien-Dindo classification of postoperative complications.[28] Death was included if it occurred within 30 days after surgery or during hospital stay. The following complications were specifically assessed: postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE) and postoperative pancreatic hemorrhage (PPH). For the different degrees of severity, the official definitions of the International Study Group of Pancreatic Surgery (ISGPS) were used.[29—31] It has to be mentioned that during the study period the former definition of POPF was applicable and was used.[32] Other specific complications included postoperative pancreatitis, hypoglycemia (blood glucose $\leq$60 mg/dl), days with blood glucose $\geq$200 mg/dl, postoperative diabetes (fasting blood glucose $\geq$126 mg/dl), and exocrine insufficiency (repetitive substitution of pancreas enzymes). Surgical site infections were diagnosed according to the Centers for Disease Control and prevention (CDC) definition.[33] Readmission was only counted as such if it took place within 30 days after initial discharge and was related to a postoperative problem.

2.6. Statistical analysis

All outcomes were compared between the CP and pre-CP group. No imputation of missing values was performed, and

missing values were not counted in the analyses. Dichotomous variables were evaluated with the chi-square test. Ordinal variables were evaluated with student's t-test if normally distributed and the Mann-Whitney-U-test if not normally distributed. Respecting the fact that some variables were non-normally distributed, we used the median for the description. In the case of normally distributed variables, we used mean. P-values <0.05 were considered statistically significant. There was no adjustment for multiple testing. For all statistical analyses, SAS 13.2 was used.

3. Results

3.1. Patients' characteristics

During the study period, 295 patients underwent pancreatoduodenectomy, of which 147 were in the pre-CP and 148 in the CP group (Table 1). Fig. 1 summarizes the patient recruitment and group allocation. Regarding demographic and clinical characteristics, the firmness of pancreas tissue, the amount of portal vein resections and the preoperative hemoglobin level differed significantly between the two groups. The pancreas tissue was softer in the pre-CP group with 84 patients, and 69 patients in the CP group ($p = 0.04$). Twenty-three patients received a portal vein resection in the pre-CP, compared to elven in the CP group ($p = 0.02$). Preoperative hemoglobin level was 12.4 g/dl in the pre-CP and 12.8 g/dl in the CP group ($p = 0.04$). The underlying condition for which resection was performed did not differ between the groups.

3.2. Process quality

The comparison of measures of process quality is presented in Table 2. Central venous catheters, arterial catheters, foley catheters and abdominal drainages were removed significantly earlier in patients treated with CP. Likewise, the days of first intake of liquids, liquid nutritional supplement and solids, did change after CP implementation, with earlier intake in the CP group. The postoperative day of first and second determination of pancreas enzymes in drainage liquids differed significantly between groups, as more patients in the CP group underwent enzyme determination on the recommended days. Usage of incentive spirometers did not increase following CP implementation.

3.3. Outcome quality

The results regarding outcome quality are presented in Table 3. In the pre-CP group, seven patients died due to multi-organ failure, one due to post-pancreatectomy hemorrhage and one due to pulmonary failure caused by fulminant aspiration pneumonia. Causes for multi-organ failure were four times sepsis due to bowel leakage, two mesenteric infarctions, and two fatal hemorrhages. After CP implementation five patients died due to multi-organ failure: two caused by bowel necrosis due non-occlusive mesenteric ischemia, one caused by postoperative hemorrhage near the pancreatojejunostomy, and two due to sepsis. One of these patients suffered from POPF Grade C.

There were three significant differences between groups. The number of patients with exocrine insufficiency dropped significantly after CP implementation (47.3% vs. 69.7%, $p < 0.0001$). The median number of days with maximum pain level greater than three was significantly higher with three days in the CP group and one day in the pre-CP group ($p < 0.0001$). The proportion of patients receiving intraoperative red blood cell concentrates (RBCC) dropped significantly after CP implementation (26.7% vs. 10.8%, $p = 0.0005$). The mean number of transfused RBCC was higher in the pre-CP group (2.83 compared to 1.46), and the difference was nearly significant ($p = 0.05$). Regarding postoperative morbidity and mortality, there were no differences between the two groups, neither for the summary measures nor for specific complications. Length of stay did not relevantly differ between patients treated with and without CP, and the discharge goal stipulated in the CP was not met.

4. Discussion

This study evaluated the effect of implementation of a CP for pancreatoduodenectomy on various parameters of perioperative process and outcome quality. Pancreatic surgery is complex and should only be performed by experienced and specialized surgeons in a dedicated setting. In the last decades, perioperative mortality has dropped, but morbidity remains high.[1,34–36] This might partly be explained by the fact that older patients with significant comorbidities or locally advanced tumors are resected. Yet, a lack of standardization of perioperative treatment might contribute to high morbidity.[37–39] Therefore, the principal aim of this study was to show if CP implementation led to improvement and standardization of the perioperative treatment pattern and consequently lower morbidity in patients undergoing pancreatoduodenectomy. While a number of studies from Anglo-Saxon countries have shown such effects, the corresponding evidence from continental Europe is scarce.[16] Therefore, we chose to conduct a study in a tertiary care center in Germany.

We observed an improvement for many parameters of process quality, while some specific parameters remained unchanged after CP implementation. The CP served as an excellent instrument to standardize the timing of postoperative pancreas enzyme measurement in drainage fluid. This is important for a timely diagnosis of possible postoperative pancreatic fistula, one of the most frequent and relevant complications after pancreatoduodenectomy. At the same time the risk of drain-related ascending infection or enteral fistula increases with the time of drain indwelling, so that timely drain removal is recommended once drain fluid shows no increased enzyme levels.[40–42] After CP implementation, the median day of drain removal changed significantly from postoperative day eight to six (<0.0001). The risk of ascending infections also pertains to other indwelling catheters. Therefore, they should be removed as soon as possible if clinical conditions permit.[43–45] In our study, removal of nearly all catheters took place significantly earlier after CP implementation. Only the median day of epidural catheter removal and the

Table 1 Characteristics of the study groups.

Patient characteristic	Pre-CP group (n = 147) %	CP group (n = 148) %	p-value
Mean age (years)	64.2	65.6	0.31
Sex			0.78
Male	87 (59.2)	90 (60.8)	
Mean BMI (kg/m^2)	25.7	25.6	0.89
ASA score			0.70
I	6 (8.0)	11 (7.5)	
II	39 (52.0)	71 (48.3)	
III	27 (36.0)	65 (44.2)	
IV	3 (4.0)	0	
X	72 (49.0)	1 (0.7)	
Diabetes	35 (23.8)	35 (23.7)	0.97
Operation			0.30
PPPD	124 (84.4)	131 (88.5)	
Kausch-Whipple	23 (15.6)	17 (11.5)	
Consistency of pancreas tissue			0.04*
Soft	84 (57.1)	69 (46.6)	
Hard	18 (12.2)	34 (30.0)	
X	45 (30.6)	45 (30.4)	
Type of anastomosis			0.40
Pancreaticojejunostomy	90 (61.2)	106 (71.6)	
Pancreatogastrostomy	44 (30.0)	42 (28.4)	
X	13 (8.8)	0 (0)	
Portal vein resection	23 (15.6)	11 (7.4)	0.02*
Multivisceral resection	15 (10.2)	24 (16.2)	0.12
X	(0)	2 (0.14)	
Diseases for which pancreatoduodenectomy was performed			
Ductal Adenocarcinoma	61 (41.5)	49 (33.1)	
Adenocarcinoma of the duodenum	2 (1.3)	2 (1.3)	
Adenocarcinoma of ampulla of *Vateri*	6 (4.1)	2 (1.3)	
Cholangiocarcinoma	25 (17.0)	29 (19.6)	
Chronic pancreatitis	28 (19.0)	26 (17.6)	
IPMN	6 (4.1)	15 (10.1)	
Others	19 (12.3)	24 (16.2)	
Preoperative mean albumin (g/l)	34.4	34.2	0.81
Preoperative mean hemoglobin (g/dl)	12.4	12.8	0.04*
Preoperative mean glucose (mg/dl) [range]	137.0 [44–424]	138.9 [54–406]	0.57
Median operation time (min) [range]	375.0 [230–634]	371.5 [220–728]	0.58
Median number of resected lymph nodes [range]	13.0 [1–46]	14.0 [0–47]	0.25

BMI= Body-Mass-Index; ASA = American Society of Anesthesiology; X = missing data; Pre-CP group = Pre-Clinical pathway group; CP group = Clinical pathway group; PPPD = pylorus-preserving pancreatoduodenectomy; dignity others Pre-CP-Group = in declining order: four duodenal adenomas, three duodenal ulcer, three metastasis, two neuroendocrine tumors, two microcytic adenomas, one pancreatic intraepithelial neoplasia, one microcytic intraepithelial neoplasia, one trauma, one pancreatic pseudocyst and one leiomyoma of the incisive papilla region; dignity others CP-Group = in declining order: six duodenal adenomas, five microcytic adenomas, four metastasis, three pancreatic pseudocyst, two traumas, one choledochal cyst; one pancreatic intraepithelial neoplasia, one non Hodgkin lymphoma and one acinar cell carcinoma; g/l = gram/liter; g/dl = gram/deciliter; mg/dl = milligram/deciliter; min = minutes; * = p-value $\leq$ 0.05.

median day of nasogastric tube removal did not show a significant change after CP implementation. Early enteral nutrition, as compared to prolonged fasting, has been shown to be associated with lower mortality and shorter hospital stay in a meta-analysis.[46] We could observe a significant reduction of median day of first intake of liquids and solids after CP implementation. In contrast to these encouraging findings, process quality regarding one parameter did not improve after CP implementation. The frequency of incentive spirometer usage was significantly lower after CP implementation, with about a quarter of patients not having used a spirometer postoperatively (p = 0.01). Incentive spirometers are a valuable and easy-to-use means to lower the risk of acquiring pneumonia.[47] The reasons for their apparent underutilization in patients treated with a CP which clearly stipulated spirometer usage are not evident. The finding is particularly irritating because almost all patients treated during the same time period with a CP for distal or total pancreatectomy used a spirometer.[48]

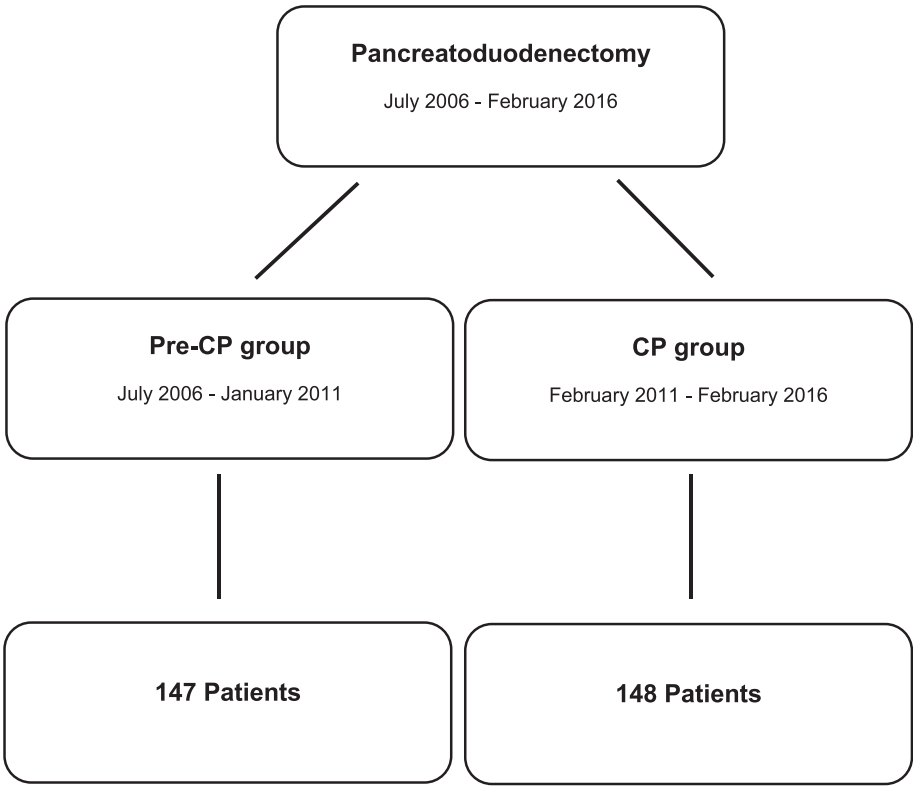

Figure 1 Flowchart of patient recruitment. The two groups comprised all patients consecutively operated during the respective study period. Pre-CP group = Pre-Clinical pathway group; CP group = Clinical pathway group.

Concerning postoperative complications and mortality, the analyses did not show a difference between patients treated before and after CP implementation. In the literature, mortality is often measured only as 30-day mortality rate.[49,50] However, due to modern intensive care as well as an improvement in interventional techniques, patients might succumb to late or secondary complications well after 30 days from the index operation.[50] Using CDC recommendations, we considered in-hospital mortality, which was 4.7% in the CP and 6.1% in the pre-CP group, rather than 30-day mortality. These figures are within the range of other series reporting 30-day mortality.[51,52] Compared to other studies, the overall postoperative morbidity in our patients seems high.[53] A possible reason is the meticulous use of the Clavien-Dindo-classification for postoperative complications. This classification counts every deviation from the normal postoperative course as complication, while many studies reporting complications have not used a dedicated classification or lack a detailed definition for complications.[28,54] The consistency of pancreas tissue as well as the underlying condition can influence the leakage rate of pancreas anastomoses. In our study the tissue consistency was significantly softer in the pre-CP group, but the incidence of specific complications, such as postoperative pancreatic fistula, did not change significantly after implementation of the CP. The medical indications for pancreatic head resection did not differ between the groups.

Nearly two years after CP implementation at our institution, Lassen et al. published guidelines for perioperative care for pancreaticoduodenectomy under the auspices of the Enhanced Recovery After Surgery (ERAS ®) society.[55] Evidence is summarized and recommendations are given for 27 care items in comparison to our CP which contains 23 care items. Sixteen recommendations are very similar between the two documents, while in 10 cases recommendations are given by the ERAS guideline which aren't represented in our CP. Examples are the use of wound catheters or transversus abdominis plane (TAP) block, preanesthetic medication, oral bowel preparation, perioperative oral immunonutrition, perioperative biliary drainage and postoperative nausea and vomiting (PONV) prophylaxis. In contrast, our CP comprises recommendations regarding surgical technique, invasive drains and catheters, oral analgesia, transfusion and nursing, which are not contained in the ERAS guidelines. As mentioned above, CPs involve all different disciplines that are part of the treatment team and aim to translate evidence into clinical practice. A potential revision of the CP should consider the evidence-based ERAS guidelines.

Literature describes intraoperative and postoperative transfusion as independent risk factors associated with decreased disease-free survival in patients who underwent pancreas head resection for pancreatic adenocarcinoma.[56] It is also stated that intraoperative transfusion is an independent negative prognostic factor for survival after pancreatoduodenectomy for patients with periampullary cancers.[57] After CP implementation, the proportion of patients receiving intraoperative RBCC transfusion dropped significantly, with 26.7% in the pre-CP and 10.8% in the CP group ($p = 0.005$). Furthermore, the mean number of intraoperative and postoperative transfused RBCC dropped

Table 2 Parameters of process quality.

Patient characteristic	Pre-CP group (n = 147) %	CP group (n = 148) %	p-value
Somatostatin administration (at least once)	103 (70.1)	103 (69.6)	0.93
Antibiotic prophylaxis	134 (99.2)	147 (99.3)	1.0
Peridural analgesia	136 (92.2)	138 (93.2)	0.97
Central venous catheter	140 (97.2)	145 (98.6)	0.44
Arterial catheter	128 (97.7)	142 (97.9)	1.0
Usage of incentive spirometer	116 (87.9)	112 (76.2)	0.01*
X	15 (10.2)	1 (0.7)	
Median day of PDA catheter removement	5.0	4.0	0.17
Median day of central venous catheter removement [range]	7.0 [0—51]	6.0 [1—19]	0.02*
Median day of arterial catheter removement [range]	2.0 [0—14]	2.0 [0—6]	0.01*
Median day of foley catheter removal [range]	4.0 [0—30]	4.0 [1—77]	0.03*
Median day of nasogastric tube removal	2.0	2.0	0.06
Number of patients with nasogastric tube	87 (67.0)	47 (32.0)	
Median day of drain removal [range]	8.0 [4—51]	6.0 [3—83]	<0.0001*
Median day of first measurement of pancreas enzymes	1.0 [0—3]	3.0 [1—9]	<0.0001*
Median day of second measurement of pancreas enzymes [range]	2.0 [1—7]	5.0 [2—19]	<0.0001*
Median day of first intake of liquids [range]	1.0 [0—4]	1.0 [0—3]	<0.0001*
X	20 (13.6)	4 (2.7)	
Median day of first intake of liquid nutritional supplement	3.0 [1—11]	2.0 [1—12]	<0.0001*
X	42 (28.6)	12 (8.1)	
Median day of first intake of soft diet [range]	4.0 [1—18]	3.0 [2—12]	<0.0001*
X	42 (28.6)	30 (20.3)	
Median day of first intake of full diet [range]	7.0 [3—43]	4.0 [2—15]	<0.0001*
X	44 (30.0)	5 (3.4)	
Median day of first mobilization to edge of the bed [range]	1.0 [0—4]	1.0 [0—4]	0.79
X	18 (12.2)	6 (4.1)	
Median day of full mobilization [range]	2.0 [1—27]	2.0 [1—21]	0.63
X	26 (17.7)	7 (4.7)	

Pre-CP Group = Pre-Clinical pathway group; CP group = Clinical pathway group; PDA = peridural anesthesia; X = missing data; * = p-value $\leq$ 0.05.

Table 3 Parameters of outcome quality.

Patient characteristic	Pre-CP-Group (n = 147) %	CP-Group (n = 148) %	p-value
Readmission	6 (4.1)	10 (6.8)	0.31
30-day mortality	5 (3.4)	3 (2.0)	0.50
Postoperative morbidity according to Clavien-Dindo-Classification			0.08
Grade 0	33 (22.5)	34 (23.0)	
Grade I	7 (4.8)	15 (10.1)	
Grade II	68 (46.3)	53 (35.8)	
Grade IIIA	14 (9.5)	20 (13.5)	
Grade IIIB	15 (10.2)	14 (9.5)	
Grade IVA	0	5 (3.4)	
Grade IVB	1 (0.7)	0	
Grade V (in-hospital mortality)	9 (6.1)	7 (4.7)	
POPF			0.17
Grade A	6 (4.1)	10 (6.8)	
Grade B	15 (10.2)	13 (8.8)	
Grade C	6 (4.1)	13 (8.8)	
DGE			0.20
Grade A	23 (15.7)	34 (23.0)	
Grade B	14 (9.5)	9 (6.1)	
Grade C	6 (4.1)	10 (6.8)	
PPH			0.07
Grade A	0	5 (3.4)	
Grade B	4 (2.7)	5 (3.4)	

(*continued on next page*)

Table 3 (*continued*)

Patient characteristic	Pre-CP-Group (n = 147) %	CP-Group (n = 148) %	p-value
Grade C	10 (6.8)	5 (3.4)	
Discharge with drain	11 (8.7)	7 (4.9)	0.22
Insulin administration (at least once)	57 (43.2)	71 (48.6)	0.36
Postoperative diabetes	8 (5.4)	15 (10.1)	0.13
Hypoglycemia (blood glucose ≤60 mg/dl)	18 (13.2)	14 (9.6)	0.33
Median number of days with blood glucose ≥200 mg/dl [range]	1 [0—43]	0 [0—55]	0.32
Exocrine insufficiency	99 (69.7)	70 (47.3)	<0.0001*
Revisional surgery	24 (16.3)	23 (15.5)	0.85
Median intraoperative blood loss (ml) (IQR)	800.0 (1200—500)	825.0 (1300—500)	0.32
Patients received intraoperative RBCC transfusion	39 (26.7)	16 (10.8)	0.0005*
Mean number of intraoperative transfused RBCC [range]	2.83 [0—10]	1.46 [0—6]	0.05
Patients received postoperative RBCC transfusion	49 (33.3)	40 (27.0)	0.20
Mean number of postoperative transfused RBCC [range]	6.3 (0—80)	4.2 (0—24)	0.14
Median number of days with highest pain level > 3 [range]	1.0 [0—16]	3.0 [0—50]	<0.0001*
X	73 (49.6)	1 (0.7)	
Analgesics requested (Mean number of supplemental requested doses during hospital stay) [range]	0.24 [0—1.54]	0.31 [0—2.25]	0.31
Median day of first defecation	4.0	3.0	0.26
Discharge			0.54
Home	132 (89.8)	129 (87.2)	
Other hospital	2 (1.4)	4 (2.7)	
Rehabilitation	4 (2.7)	8 (5.4)	
Median length of stay on IMC [range]	3.0 [0—61]	3.0 [0—55]	0.15
Median length of stay on ICU [range]	2.0 [0—27]	1.0 [0—31]	0.74
Median length of stay [range]	18.0 [9—141]	17.0 [8—94]	0.20
Median length of postoperative stay [range]	15.0 [8—129]	14.0 [7—90]	0.12

Pre-CP-Group = Pre-Clinical pathway-Group; CP-Group = Clinical pathway-Group; POPF= Postoperative pancreatic fistula; DGE = Delayed gastric emptying; PPH= Postoperative pancreatic hemorrhage; postoperative diabetes = fasting blood glucose level higher than 126 mg/dl; IMC= Intermediate care unit; ICU= Intensive care unit; RBCC = red blood cell concentrate; Rehab = Rehabilitation; IQR = interquartile range; * = p-value ≤ 0.05.

after CP implementation (Table 3). In contrast to the encouraging findings of improved process quality, outcome quality regarding one parameter deteriorated after CP implementation. The number of days with a relevant pain level was in fact higher in the CP group. This finding is rather surprising, because the CP contained a dedicated analgesia scheme according to recent recommendations. It included epidural catheter placement, which was carried out in the overwhelming majority of patients. Additional oral analgesics were administered in a stepwise, pain-adjusted manner, so that there is no obvious explanation for higher pain levels in patients treated according to the CP. One potential explanation, although merely hypothetical, could be that nursing staff had increased awareness for possible postoperative pain after CP implementation and tended to assess patients more meticulously regarding their pain, inciting a higher reported pain level. This would be a form of ascertainment bias. Additional analgesic requests by patients also occurred with the same frequency as in patients treated without CP, which indicates that the stipulated analgesic therapy was rather sufficient. Delayed mobilization and insufficient pain control can have relevant consequences for the patient, because of an unduly increased length of stay and an increased risk of postoperative morbidity especially with regard to pulmonary complications.[58]

One of the aims of CP implementation is to avoid unnecessarily long hospital stays without a clear medical reason by means of streamlining perioperative processes. In this study, length of stay did not decrease after CP implementation, and still showed a relevant variation between single patients. However, length of stay in larger series in

the literature was rather in the range of what we observed before and after CP implementation than in the range of the goals set in our CP, which might have been too ambitious.[59] Moreover, the analyses comprised all consecutive patients including those with relevant complications, which explains the large variation and exceedingly long hospital stay in some patients.

The study has a number of methodological limitations. It is retrospective and relied on chart review for data collection. All clinical results are potentially subject to bias by the different time periods of assessment. Therefore, the validity of data could be inferior to prospectively collected data. Moreover, for some variables values for single patients were not documented and not used for the analyses. This might bias the results, although there is no reason to assume that variables were selectively not recorded. Unfortunately, comprehensive survival data for all patients operated during the ten-year study period are missing. Obviously, surgical technique and the skills and experience of the single surgeon do affect perioperative outcomes.[36] During the study period, a number of different surgeons operated on patients and surgical performance bias can't be excluded. Most of these limitations would have been overcome by designing the study as randomized controlled trial, which is however hardly feasible to conduct when evaluating clinical pathway usage.[37] The methodological strength of our study was that patients were included according to the "intention-to-treat" principle. All consecutive patients undergoing pancreatoduodenectomy before and after CP implementation were included. Even if certain goals of the CP such as mobilization or resumption of diet were not met, patients were not taken "off the pathway". Moreover, patients were analyzed regardless of possible complications. Consequently, selection bias can virtually be ruled out. We believe this approach to be the only valid way for evaluating the true clinical impact of CPs because it represents clinical reality, where CPs are meant to be a tool for treating the entirety of patients with a specific intervention or condition.

5. Conclusion

In conclusion, this study showed that a CP for pancreatoduodenectomy can affect several aspects of perioperative care. CP usage fulfilled the expectations regarding a high degree of treatment standardization. Drain management and the uptake of liquids and solids were improved. Other expected improvements, such as earlier mobilization, better pain control, and shorter length of stay, were not realized after CP implementation. Outcome parameters such as morbidity and mortality did not differ between patients treated with and without CP. CPs in pancreatic surgery can be used to facilitate some perioperative processes, but their utility must be weighed against the expected cost and efforts of implementation.

Conflict of interest

The authors declare that they have no conflict of interest.

All procedures in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Informed consent

According to the decision of the medical ethical committee no informed consent was required.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2019.10.003.

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