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EDITORIAL

Current Status of Fast-Track Recovery Pathways in Pancreatic Surgery

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Summary

Context Pancreatic surgery is often associated with significant morbidity, thus requiring high level of peri-operative care and long hospital stay. Multi-modal "enhanced recovery" or "fast-track" pathways have recently been introduced, aiming to expedite patient recovery. **Objective** To evaluate the evidence underpinning the use of fast-track pathways in the peri-operative care of patients undergoing pancreatic cancer surgery. **Results** The available evidence is limited**,** consisting of three retrospective studies that report median length of hospital stay between 7 and 13 days. No significant difference has been noted in re-admission or 30-day mortality rates between fast-track patients and historical controls, but there is a trend for higher overall complication rate for the fast-track groups. **Conclusion** Implementation of an enhanced recovery pathway is feasible and can achieve shorter hospital stay and reduced costs, with no increase in re-admission or peri-operative mortality rates. There is, however, conflicting evidence on the physiological mechanisms that contribute to accelerated patient recovery. Certain safety issues associated with post-operative morbidity warrant rigorous evaluation in further prospective studies.

Introduction

Since Whipple *et al*. popularised pancreaticoduodenectomy in 1935 [1], pancreatic resections are increasingly being performed for treatment of pancreatic tumours, especially during the last two decades [2]. In the United Kingdom, the annual number of pancreaticoduodenectomies has increased by 71% during the last 7 years [3]. Peri-operative morbidity and mortality rates are improving with increasing experience in large-volume tertiary centres [4]. Recently, however, parameters such as duration of hospital stay and length of patient recovery appear to attract increasing attention from both patients and health care providers, altering the standards and targets. "Enhanced recovery" or "fast-track" programmes have been introduced in the field of peri-operative care, representing multi-modal strategies that provide for optimal pain relief, stress reduction with regional anaesthesia, early enteral nutrition and patient mobilisation [5]. These regimes aim to restore the functional capacity of surgical patients to their pre-morbid state faster and more effectively than the conventional peri-operative approaches and their favourable effect has already been demonstrated in colorectal cancer surgery [6, 7]. In pancreatic surgery, the duration of hospital stay depends on post-operative surgical complications such as pancreatic leaks, intra-abdominal collections, haemorrhage, delayed gastric emptying and general medical complications involving the cardiopulmonary systems. Therefore, peri-operative interventions aiming to minimise the above adverse events could potentially expedite patient recovery and improve outcomes.

Key words Economics; Mortality; Pancreas; Pancreaticoduodenectomy; Perioperative Care; Rehabilitation

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Aims and Methods

This review aims to present the evidence underpinning the use of multi-modal fast-track pathways in pancreatic cancer surgery. Key elements of these protocols are presented, evaluating their feasibility, safety and efficacy in accelerating patient recovery. Bibliographic search in the MEDLINE®, (http://www.ncbi.nlm.nih.gov/pubmed/) EMBASE®, (http://www.embase.com/) CINAHL® (http://www.ebscohost.com/cinahl/) databases and the Cochrane Collaboration Library (http://www.cochrane.org/)was performed to retrieve all relevant publications in English language to date. The terms "clinical pathway", "fast track", "enhanced recovery", "peri-operative", "pancreas" and their derivatives such as "pancreatic", "pancreaticoduodenectomy", "Whipple's", "resection", "surgery" and synonyms were used in various combinations. Backward referencing by manual search of bibliography was also performed to increase the yield of papers. Studies were included if

they involved clinical pathways used in a hospital setting to facilitate the care of adults undergoing elective surgery for pancreatic malignancy. Studies with sufficient description of the content of the clinical pathway and reporting clinically relevant outcome measures, such as length of hospital stay, complication rate, 30-day re-admission rate and 30-day mortality rate, were included. Studies were excluded if they described single interventions in one parameter of peri-operative care rather than a bundle of measures that constitute the "fast-track" or "enhanced recovery" programmes; the evidence that established each individual element as part of the pathway lies beyond the aim of this review.

Results

Enhanced-recovery programmes have only recently been introduced in gastrointestinal cancer surgery; hence the available evidence related to pancreatic resections is limited. A total of six publications were retrieved during our search [8, 9, 10, 11, 12, 13], three of which were excluded from this analysis, because they did not provide sufficient details of the clinical pathway components [8, 9], or were concerned only with isolated elements of peri-operative care [10]. Three retrospective case-series satisfied the inclusion criteria, two of which had comparisons with historical controls.

Kennedy *et al*. [11] retrospectively reviewed the outcomes of 135 consecutive pancreaticoduodenectomies, classified in two groups; a "post-pathway group" of 91 patients, who underwent pancreaticoduodenectomy after implementation of a clinical pathway (Table 1), compared to a "pre-pathway" group of 44 patients. Both groups were similar regarding demographic data (age, gender and race) and underlying pathology (percentage of malignant cases). During the post-pathway period higher volume of operations was

Table 1. Summary of fast-track pathway elements in each study.

Days	Kennedy *et al*., 2007 [11]	Berberat *et al*., 2007 [12]	Balzano *et al*., 2008 [13]
Pre-op	Preoperative heparin, 5,000 units s.c.. Tromboembolic deterrent stockings and sequential compression devices		At the time of informed consent to operation patient informed about fast-track rehabilitation programme.
Day 0	Perioperative antibiotics. Central access per anaesthesia assessment. Nasogastric tube after induction of anaesthesia. Two drains (one on each side). Night of operation spent in ICU setting. Intravenous patient-controlled analgesia, proton pump inhibitor (PPI). b-blockade orally pre-op or i.v. intra-operatively.	Single shot of antibiotic prophylaxis. Weight-adapted thrombosis prophylaxis wit low molecular-weight heparin and compression stockings. Nasogastric tube and intra-abdominal drains routinely. First night in ICU or intermediate care unit.	Analgesia: thoracic epidural (T7-T9 level) continuous infusion of bupivacaine 0.125% + fentanyl 2 μg/ml at a rate of 4-6 mL/h until day 5, plus i.v. paracetamol or NSAIDs, or, if epidural catheter is contraindicated, patient-controlled analgesia with morphine, plus i.v. paracetamol or NSAIDs.
Day 1	Removal of nasogastric tube, discontinuation of antibiotics. Sips of water and ice chips at rate ≤30 mL/h. Out of bed ambulating, discontinuation of sequential compression devices. Tromboembolic deterrent stockings and heparin subcutaneously. Intravenous b-blockers and PPI and transfer to ward.	<u>Pancreatic secretion inhibitor:</u> Octreotide, 300-600 μg/day x 5-7 days. <u>Postoperative pain treatment:</u> Peridural or patient-controlled analgesia wit stepwise dose reduction and transition to nor opioid medication (metamizol 0.5-1 g/day QDS or paracetamol 0.5-1 g/day QDS).	Removal of nasogastric tube if drainage amount <300 mL. Mobilization out of bed for more than 1 h. Intravenous fluid administration (30 mL/kg per day of crystalloids plus 5% glucose) continued until adequate oral fluid intake.
Day 2	Clear liquid diet. Remove Foley catheter. Minimize all i.v. fluids, Begin diuresis and continue until discharge or patient reaches preoperative weight. Continue tromboembolic deterrent stockings, subcutaneous heparin, b-blockade, and PPI until hospital discharge.	Metoclopramide (60 mg/day), magnesium (200 mg/day) and lactulose (3x10 g/day) to support early start of normal bowel function which is stopped with the first stool. Clear fluids orally 6 hours post extubation.	Enhanced mobilization (more than 2 h out of bed).
Day 3	Regular diet with pancreatic enzymes.	Stepwise oral intake increase: liquid, mashed light diet, normal food.	Clear fluid intake (free amount). Enhanced mobilization (more than 4 h out of bed, with personal hygiene care in bathroom)
Day 4	All medications orally, discontinue all i.v. fluids. Remove drain with lowest volume (if appropriate).		Solid food intake.
Day 5	Remove remaining drain (if appropriate). Distribute pre-printed discharge instructions. Medical oncology and radiation oncology consults (if appropriate).		Diet increase on daily basis (given as 5 to 6 small meals) until reaching a calorie intake of 1,000 kcal on day 8. Drain removal (if no pancreatic or biliary fistula, when daily amount <200 mL). Epidural catheter out.
Day 6	Discharge home.		
Discharge	Arrange follow-up appointment for 4 weeks after discharge. Discharge medications: PPI, pancreatic enzymes, analgesics.		Absence of fever (<37·5°C for more than 48 h), adequate pain control with oral analgesics, ability to take solid foods (at least 1,000 kcal/day), passage of stools, adequate mobilization and acceptance of discharge by patient.

QDS: four times a day

undertaken (mean 7.6 cases/month) comparing to the previous period (2 cases/month), which reflected a centralization of pancreatic services in this hospital. Significantly shorter operation times (mean±SE, 379±12 min *vs*. 435±14 min for the pre-pathway patients, P<0.0001) and pre-procedure anaesthetic times (76±2 min *vs*. 95±4 min of the pre-pathway patients, P<0.0001), were noted during the same post-pathway period.

There was no significant difference in the overall peri-operative complication rate before (44%) and after (37%) implementation of the pathway. Similar rates were noted between pre-pathway and post-pathway groups with regard to the incidence of pancreatic fistula (9% *versus* 2%, respectively), delayed gastric emptying (7% *versus* 8%, respectively), wound infection (9% *versus* 13%, respectively) and less common complications, such as cardiovascular events, pneumonia, intra-abdominal abscesses requiring drainage, small bowel obstruction and deep venous thrombosis (total morbidity rates: 25% *versus* 20%, respectively). There was a significant decrease in the post-operative length of hospital stay in the post-pathway group (median 7 days) compared to the pre-pathway cohort (13 days, P<0.0001), with a parallel reduction in total hospital charges (mean±SE, $240,242±32,490 for the pre-pathway patients *vs*. $126,566±4,883 for post-pathway patients, P<0.0001). This decrease length of hospital stay did not come at the expense of higher 30-day re-admission rate (7.0% for pre-pathway patients and 7.7% for post-pathway ones).

In a retrospective review of 283 consecutive pancreatic resections, Berberat *et al*. [12] implemented the enhanced recovery pathway outlined in Table 1. Two thirds of the pancreatic resections were performed for pancreatic tumours and the remaining for benign diseases. The overall median operating time was 5 h and 45 min (range: 73 min to 10 h and 43 min). Median blood loss was 700 mL (range: 50-5,500 mL) and 26% of the patients needed blood transfusion therapy. A total 69% of patients were transferred to ICU with median stay of 1 day (range: 1-32 days), whereas 31% of patients were directly transferred from the recovery room to an intermediate care unit or even to the ward (22.4% and 8.4%, respectively). Overall, patients returned to the ward after a median of 2 days (range: 0-38 days). The mean hospital stay was 10 days (range: 4-115 days) and the 30-day readmission rate was 3.5%. Nasogastric tubes were removed from most patients immediately after the end of the operation (80.4%) or during the first postoperative day (13.3%) but 11.4% needed re-insertion of the nasogastric tube later, with a median interval to reinsertion of 6 days (range: 1-13 days). Resumption of clear oral fluid intake was possible on day 1 (median: 1 day; range: 0-6 days) and of normal food on median day 5 (range: 1-24 days). The intra-abdominal drains were removed on median day 3 (range: 0-19 days). The bladder catheter was removed on median day 5 (range: 1-49 days). Finally, the central venous line was removed on median day 6 (range: 1-49 days). Gastrokinetic drugs did not expedite bowel movement and, in fact, use of metaclopramide was associated with delayed patient discharge (P<0.05). First mobilization (out of the bed) was achieved on median day 1 (range: 0-9 days), and on median day 3 (range: 1-46 days) patients were fully mobile.

A 30-day mortality rate of 2% was noted, caused by pancreatico-jejunostomy leak (n=2), pancreatic stump leak after distal pancreatectomy (n=1), jejuno-jejunal anastomotic failure (n=1), and unexplained sepsis with multi-organ failure in one case. Surgical morbidity mounted to 24.7%, caused by delayed gastric empting (7.8%), postoperative haemorrhage (7.5%), pancreatic fistulae (4.7%), and wound infection (4.7%). Overall, 9% of patients received a re-laparotomy. Multivariate analysis identified that significant independent factors of early successful discharge were age less than 60 years (odds ratio: 4.06; P<0.001), short operating time less than 6 hours (odds ratio: 1.99; P<0.05), and early extubation (odds ratio: 2.8; P<0.05).

Recently, Balzano *et al*. [13] evaluated the impact of a fast-track protocol (Table 1) of peri-operative care in the recovery of 252 consecutive patients undergoing pancreaticoduodenectomy (fast-track group), who were compared to an equal-sized historical control group of patients operated before the implementation of the pathway (control group). The two groups were adequately matched for demographic data and underlying disease. Analysis of post-operative outcomes showed that in the fast-track group, successful removal of nasogastric tube was achieved in 95.6% of patients by day 3, although it was reinserted in 15% of patients because of either vomiting or re-laparotomy. All patients without a nasogastric tube commenced liquid intake on day 3 and oral food on day 4, although most patients failed to achieve the planned daily dietary calorie intake (1,000 kcal) during the first 8 days because of symptoms of food intolerance. There was no difference between the two groups regarding interval to first flatus (median day 3), but the first passage of stools occurred earlier in fast-track patients than in the control group (median 5 *versus* 6 days, respectively; P<0.001). There was no difference in the overall peri-operative mortality rate (3.6% for the fast-track group *versus* 2.8% for the control), the incidence of pancreatic fistula or any other intra-abdominal complication. The patients in the fast-track group had significantly lower incidence of delayed gastric emptying (3.9% *versus* 24.6% of the traditional group; P=0.004). The length of postoperative hospital stay was shorter in the fast-track group (median 13 days; range: 7-102 days) compared to control (median 15 days; range: 7-110 days; P<0.001). There was no significant difference in readmission rates, with 7.1% for fast-track patients and 6.3% for patients in the control group.

Discussion

Gastrointestinal cancer surgery involves major complex procedures requiring high level of surgical and peri-operative care and is associated with high morbidity and long hospital stay. The beneficial effect of implementation of multi-modal peri-operative pathways on outcomes of colorectal surgery (the Protocol of Enhanced Recovery After Surgery in Colorectal Surgery; ERAS protocol, http://clinicaltrials.gov/ct2/show/NCT00498290) has, expectedly, raised interest in other subspecialties of surgical oncology for potentially wider application [7]. Improved outcomes regarding length of patient hospital stay have also stimulated interest and support by health care providers because they could translate into financial benefits.

Systematic review of the literature regarding peri-operative care in pancreatic cancer surgery revealed a limited number of studies bearing low levels of evidence. Retrospective case-series and comparative case-control studies ("before-after") using historical controls have only been retrieved knowing well the inherent disadvantages of comparing patient outcomes across different time periods. It is generally accepted that implementation of such multi-modal pathways constitutes complex interventions that cannot be easily studied in the context of randomised controlled trials, because of weaknesses in developing, identifying, documenting, and reproducing the intervention [14]. The studies analysed in this review were not devoid of such problems. In the study of Kennedy *et al*. [11] the introduction of a fast-track protocol coincided with the appointment of two new surgeons with interest in pancreatic surgery and bigger operation volume; these facts could have independently contributed to improved recovery outcomes. Their group of patients, as well as those studied by Berberat *et al*. [12], were highly heterogeneous with regards to age and contained a case-mix of Whipple's and distal pancreatectomies, performed for both benign and malignant diseases, parameters that are proved to be independent determinants of outcome. Patient selection bias may also have been a potential weakness for the above comparative studies [11, 13], with allocation of healthier patients in the fast-track pathway groups, thus giving unfair advantage over the unfiltered controls.

Despite their potential weaknesses, the above studies have demonstrated that implementation of fast-track peri-operative care pathways is feasible in pancreatic surgery and can be associated with reduced length of stay, lower relevant hospital costs and no increase in morbidity, 30-day mortality or re-admission rates (Table 2). Balzano *et al*. [13] attributed the improved outcomes of the fast-track group to the initiation of early oral feeding, which resulted in lower incidence of delayed gastric emptying and earlier bowel activity in this group, compared to the traditional approach. Interestingly though, the noted reduction in length of hospital stay and related costs by Kennedy *et al*. [11] was not associated with proportionate decrease in the incidence of complications or mortality. It is therefore questionable whether the noted benefits resulted from improvements in physiological factors related to patient recovery or potentially from a more efficient discharge policy. It is also possible that patient, nurse, and physician participation in the clinical pathways may have influenced costs and outcomes independent of any intervention within the clinical pathway itself. Such a phenomenon, analogous to the placebo-effect observed in randomized clinical trials, termed as the "Hawthorne effect" [15] could still be considered as a benefit related to the use of fast-track pathways.

An area of potential concern was the high incidence of re-laparotomy noted in patients of the fast-track groups of around 9% [12, 13]. With the exception of Balzano *et al*.'s study (7.9%) [13], the rate of reoperation in these groups was significantly higher than re-laparotomy rates reported in large series of pancreatic resections, ranging between 2.0% and 2.7% [2, 8, 9]. Aetiological analysis showed that in 60% of re-laparotomies the indication was intra-abdominal haemorrhage, which was unlikely to be caused by implementation of fast-track pathway, and in 40% of cases the cause was pancreatic leak not amenable to radiological drainage [12]. This parameter warrants specific attention and should be a major end-point in future studies.

In summary, our systematic review concludes that the evidence underpinning the use of fast-track clinical pathways in the peri-operative care of patients undergoing pancreatic resection is limited. The preliminary results of a small number of retrospective

Table 2. Description of studies and summary of outcomes.

	Kennedy *et al*., 2007 [11]	**Berberat *et al*., 2007 [12]**	**Balzano *et al*., 2008 [13]**
Type of study	Case-series with historic control ("before-after")	Retrospective case-series	Case-series with historic control ("before-after")
Patients in pathway	91	283	252
Patients in control	44	n/a	252
Length of stay (days; study group *vs*. control)	7 *vs*. 13 (P<0.0001) Median values	10 (4-115) Mean value (range)	13 (7-110) *vs*. 15 (7-102) (P<0.001) Median values (range)
Morbidity rate (study group *vs*. control)	37% *vs*. 44%	24.7%	47.2% *vs*. 58.7% (P<0.01)
30-day re-admission rate (study group *vs*. control)	7.7% *vs*. 7.0%	3.5%	7.1% *vs*. 6.3%
30-day mortality rate (study group *vs*. control)	1.1% *vs*. 2.3%	2.0%	3.6% *vs*. 2.8%

studies have shown that the implementation of a fast-track multi-modal peri-operative pathway is feasible and can achieve shorter length of hospital stay and reduced relevant costs, with no increase in re-admission and mortality rates. The studies provide conflicting evidence on the physiological mechanisms that result in accelerated patient recovery and raise certain safety issues with regards to post-operative morbidity, which would require rigorous evaluation in the context of further, large-size, prospective randomised-controlled trials.

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Conflicts of interest None

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