Enhancing Patient Outcomes while Containing Costs after Complex Abdominal Operation: A Randomized Controlled Trial of the Whipple Accelerated Recovery Pathway

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BACKGROUND: This study was designed to determine whether a standardized recovery pathway could reduce post-pancreaticoduodenectomy hospital length of stay to 5 days without increasing complication or readmission rates.

STUDY DESIGN: Pancreaticoduodenectomy patients (high-risk patients excluded) were enrolled in an IRB-approved, prospective, randomized controlled trial (NCT02517268) comparing a 5-day Whipple accelerated recovery pathway (WARP) with our traditional 7-day pathway (control). Whipple accelerated recovery pathway interventions included early discharge planning, shortened ICU stay, modified postoperative dietary and drain management algorithm, rigorous physical therapy with in-hospital gym visit, standardized rectal suppository administration, and close telehealth follow-up post discharge. The trial was powered to detect an increase in postoperative day 5 discharge from 10% to 30% (80% power, $\alpha = 0.05$, 2-sided Fisher's exact test, target accrual: 142 patients).

RESULTS: Seventy-six patients (37 WARP, 39 control) were randomized from June 2015 to September 2017. A planned interim analysis was conducted at 50% trial accrual resulting in mandatory early stoppage, as the predefined efficacy end point was met. Demographic variables between groups were similar. The WARP significantly increased the number of patients discharged to home by postoperative day 5 compared with controls (75.7% vs 12.8%; $p < 0.001$) without increasing readmission rates (8.1% vs 10.3%; $p = 1.0$). Overall complication rates did not differ between groups (29.7% vs 43.6%; $p = 0.24$), but the WARP significantly reduced the time from operation to adjuvant therapy initiation (51 days vs 66 days; $p = 0.005$) and hospital cost ($26,563 vs $31,845; $p = 0.011$).

CONCLUSIONS: The WARP can safely reduce hospital length of stay, time to adjuvant therapy, and cost in selected pancreaticoduodenectomy patients without increasing readmission risk. (J Am Coll Surg 2019;228:415−424. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Abbreviations and Acronyms

DGE = delayed gastric emptying
ERAS = enhanced recovery after surgery
LOS = length of stay
PD = pancreaticoduodenectomy
POD = postoperative day
WARP = Whipple accelerated recovery pathway

Pancreaticoduodenectomy (PD), one of the most complex intra-abdominal operations, remains the standard of therapy for patients diagnosed with localized periampullary malignancy, as well as selected premalignant and benign conditions.[1] Pancreaticoduodenectomy is associated with a high morbidity rate and significant potential for perioperative mortality. Advances in surgical technique, modern perioperative care, and the centralization of PDs to tertiary care centers has reduced operative mortality to <5% in many institutions, and to <1% in some high-volume centers.[1,2] However, postoperative pancreatic fistula, delayed gastric emptying (DGE), and perioperative deconditioning frequently delay recovery and prolong hospital length of stay (LOS).[3] Even among high-volume surgeons, the median LOS after PD is 11 days nationally[4] and 13 days internationally.[5] Such a prolonged hospitalization subjects patients to significant risk for debility and iatrogenic complications, ranging from hospital-acquired infections to medical error.[6,7]

Enhanced recovery after surgery (ERAS) pathways emphasizing multidisciplinary, modern perioperative care can decrease complications, hasten recovery, shorten hospital LOS, and control costs.[8] Pancreaticoduodenectomy-specific ERAS pathways incorporating evidence-based dietary protocols, rehabilitation, and the standardization of level of care have proved effective in preventing medical error, coordinating care, and reducing median LOS to as low as 7 to 8 days at some of the highest-volume centers.[9-11] In addition, multiple groups have reported that approximately 10% of patients can be safely discharged as early as postoperative day (POD) 5, suggesting accelerated recovery is possible among a subset of post-PD patients.[2,12]

We hypothesized that, despite the constraints of recovery from a complex abdominal operation such as PD, a specialized, accelerated postoperative care pathway could facilitate the completion of in-hospital recovery after PD within 5 days. We developed the Whipple accelerated recovery pathway (WARP) for patients undergoing PD at low-to-moderate risk of perioperative complications. This WARP includes establishment of early discharge goals with patients and families, shortened ICU stay, a modified postoperative dietary and drain management algorithm, rigorous physical therapy with an in-hospital gym visit, standardized rectal suppository administration, and close telehealth follow-up after hospital discharge. In this single-center, prospective, randomized controlled trial, we evaluate whether the WARP could reduce hospital LOS without increasing readmissions or PD-associated complications compared with our standard post-PD pathway, which targets hospital discharge on POD 7.

METHODS

Trial oversight

This study was a single-center, prospective, randomized controlled trial designed and initiated by the academic investigators at the Thomas Jefferson University Hospital Department of Surgery. Institutional Review Board approval was obtained, and the trial was registered with ClinicalTrials.gov (NCT02517268). Written informed consent from all participating patients was obtained at the time of the initial preoperative surgical consultation.

Patients

Patients eligible for trial enrollment were adults (aged older than 18 years) scheduled to undergo PD at Thomas Jefferson University Hospital. Key preoperative exclusion criteria included major medical comorbidities (congestive heart failure, end-stage renal disease, oxygen-dependent COPD, hepatic cirrhosis), pregnancy, serum albumin <3 g/dL, and poor preoperative performance status as defined by "timed get up and go" >15 seconds.[13] Patients with a soft pancreas gland texture (a marker of elevated risk for postoperative pancreatic fistula formation,[14] unresectable disease (from distant metastases or locally advanced cancers), or those requiring portal or mesenteric vascular resection and reconstruction were excluded after consenting, based on operative findings. At the conclusion of PD, patients were excluded if the operation took longer than 8 hours, the estimated blood loss was >1 L, or if they were unable to be extubated promptly.

Trial design

Patients were then randomized in a 1:1 fashion to the WARP or control pathways by the Thomas Jefferson University Division of Biostatistics using computer-generated random permutated blocks. At the conclusion of the operation, eligibility was confirmed, and an administrator opened sequential, numbered, opaque envelopes containing the randomization assignments. The trial was open to accrual in June 2015 and was closed by the Thomas Jefferson University Data Safety Monitoring Board after a planned interim analysis after 50% accrual in September

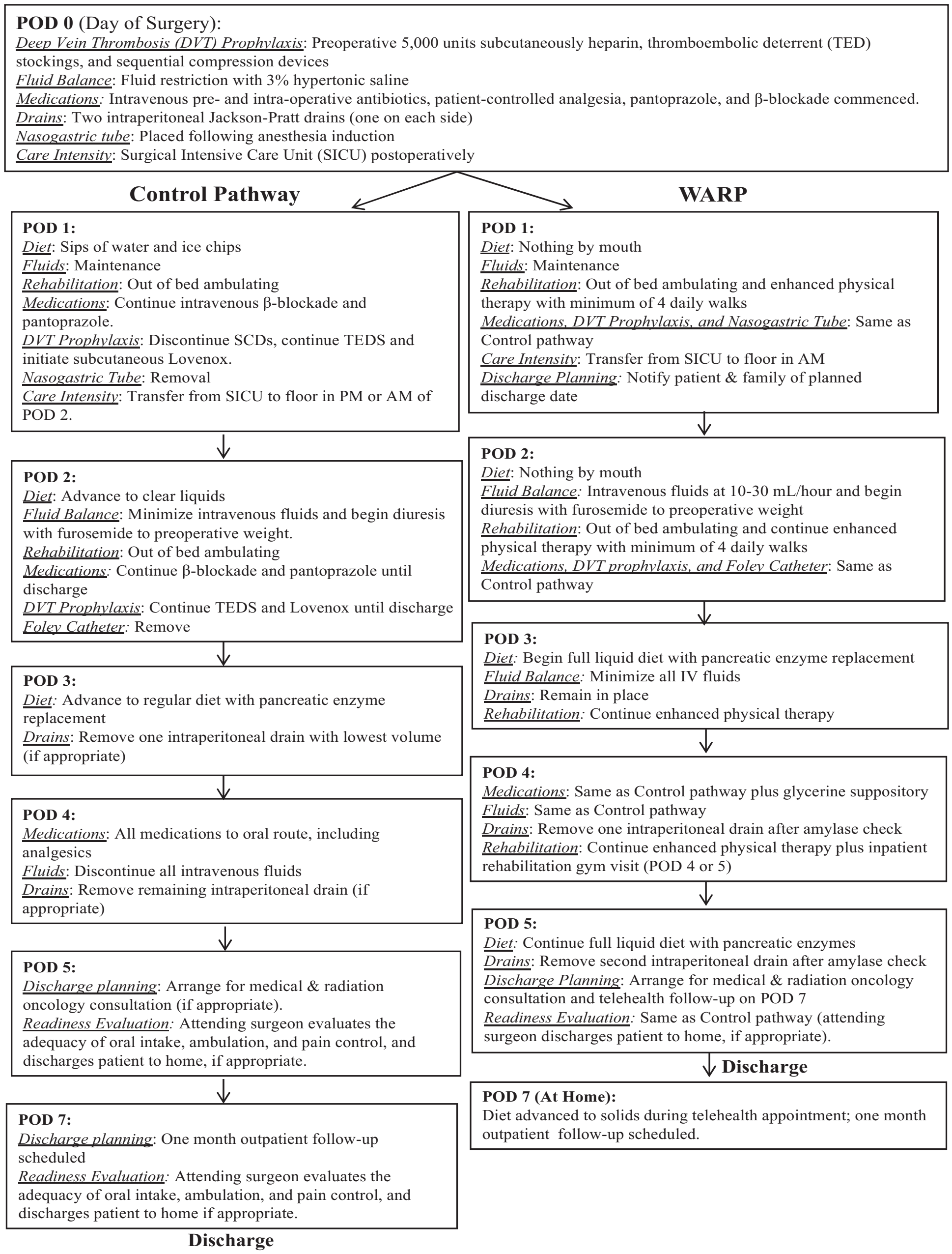

Figure 1. Control and Whipple accelerated recovery postoperative pathways. POD, postoperative day; SCD, sequential compression device.

of 2017, based on the predefined efficacy end point. The total trial duration for patient accrual was 26 months.

The postoperative control and WARP pathways are shown in Figure 1. Briefly, patients randomized to the control arm were given sips of water and ice chips on POD 1, advanced to a clear liquid diet on POD 2 and a regular diet on POD 3. The 2 intraoperatively placed Jackson-Pratt drains were removed on POD 3 and 4 based on drain character and output alone without routine amylase checks. Discharge planning was initiated on POD 5 with medical and radiation oncology consultation (if appropriate) and outpatient surgical follow-up was scheduled within 30 days. Beginning on POD 5, patients were evaluated for readiness for discharge based on the following: physiologic derangement potentially attributable to complications (eg pancreatic fistula), adequacy of oral intake, pain control, and ambulation.

In the WARP group (Fig. 1), patients were transferred from the surgical ICU to the general surgical floor on the morning of POD 1. Discharge planning was initiated thereafter with patients and their families being notified of their anticipated date of discharge (POD 5) with verbal communication, a sign in their room, and daily reminders. A full liquid diet with pancreatic enzymes was not commenced until POD 3 and subsequently continued until POD 7 (2 days after discharge). Enhanced physical therapy was initiated on POD 1, which included a minimum of 4 daily walks and a rehabilitation session in the physical therapy gym on POD 4 or 5. To mitigate the risk of subclinical pancreatic fistula, drain fluid amylase levels were assessed on a mandatory basis on POD 3, 4, or 5, just before removal of the 2 Jackson-Pratt drains. Beginning on POD 5, patients were evaluated for the readiness to discharge in a similar fashion to the control group. On POD 7 (2 days after hospital discharge), recovery status was assessed during a scheduled video or telehealth appointment, at which time a regular diet was typically resumed.

Operative intervention

Pancreaticoduodenectomy was performed by 1 of 4 experienced surgeons who specialize in pancreatectomy. On induction of general anesthesia, a nasogastric tube was placed. No patients received epidural anesthesia. The perioperative resuscitation followed best practices with a moderately restrictive fluid regimen of 3% hypertonic saline according to the HYSLAR protocol.[2] The attending surgeon commenced a midline laparotomy to evaluate for resectability and later palpated the pancreas to determine its texture (soft [normal] vs hard [fibrotic]).

Preference was given to a pylorus-preserving approach, although classic PD was performed if indicated for oncologic purposes. Intestinal anastomoses were completed using standard, hand-sewn techniques. The pancreaticojejunostomy was constructed using either an invagination or duct to mucosa technique according to the standard preference of the attending surgeon. Two Jackson-Pratt intraperitoneal drains were routinely placed adjacent to the pancreatic and biliary anastomoses in all patients and managed postoperatively as shown in Figure 1. Additional details of our standard approach to PD can be found in our other publications.[15,16]

Evaluation of outcomes

The primary end point of this trial was the percentage of patients discharged by POD 5. Secondary outcomes included complications, readmissions, time to adjuvant therapy commencement, and total hospital charges (price set by the hospital for the items and services provided to the patient) and cost (total of the direct and indirect expense for the care provided to the patient). Complications contributing to this secondary end point included: pancreatic fistula, DGE, intra-abdominal abscess, wound infections, urinary tract infections, as well as cardiac, renal, and pulmonary complications. Pancreatic fistula and DGE were defined according to the International Study Group on Pancreatic Fistula[17] and the International Study Group on Pancreatic Surgery[18] standards, respectively. Centers for Disease Control guidelines were used to define wound infections, urinary tract infections, and pneumonia (pulmonary complications).[19] Cardiac and renal complications were defined by the standards of the American Heart Association[20] and the Acute Dialysis Quality Initiative,[21] respectively.

Complications were recorded in real time on preprinted cards by the participating attending surgeons and submitted to the principal investigator (HL) on discharge. Data were subsequently verified through review of the medical record, recorded in the trial database alongside additional clinical data, and finally reported to the Jefferson Data Safety and Monitoring Board. Patients were evaluated in the office 4 weeks after discharge, and all complications noted in the outpatient office, necessary outpatient procedures, or readmissions were reported for 30 days postoperatively.

Data analysis

The trial was powered to detect an increase in POD 5 discharge from 10% to 30% with 80% power with a 2-sided $\alpha = 0.05$ using Fisher's exact test. A predefined interim analysis was planned at 50% accrual. Power was estimated via simulation assuming an O'Brien-Fleming α-spending function. For 80% power, a sample of 142 randomized subjects was required. The nominal p value for stopping for efficacy was $p < 0.00506$, with a final p value boundary of 0.04553 if the study did not stop for efficacy. In simulation, the trial stopped early for efficacy 16.2% of the time, assuming the true discharge rate in the intervention arm was 30%. The actual interim analysis was performed with data from 70 of 142 patients (information fraction 0.493). The nominal p value bound at that information fraction was $p < 0.00305$. Safety was monitored using a Bayesian stopping rule where the intervention would be deemed unsafe if the posterior probability that the readmission rate in the 5-day arm exceeded the readmission rate in the control arm by more than 5% was >90%. The historical rate of readmission at Thomas

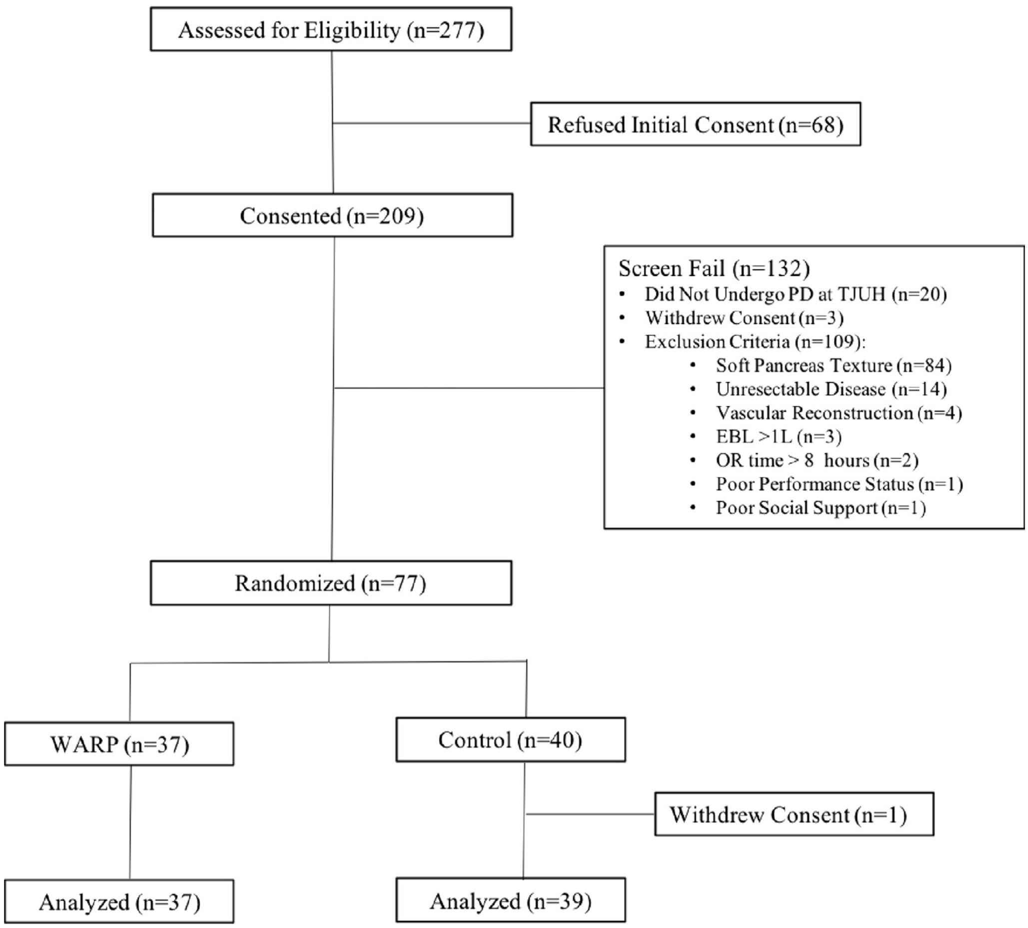

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. EBL, estimated blood loss; OR, operating room; PD, pancreaticoduodenectomy; TJUH, Thomas Jefferson University Hospital; WARP, Whipple accelerated recovery pathway.

Jefferson University was estimated at 15%. The priors specified were $\beta(0.2,0.8)$ for the intervention arm and $\beta(15,85)$ for the control arm. That is, the rate in under the 5-day protocol was assumed to be 20%, but with fairly high uncertainty (equivalent to data from 1 patient), and the rate under control was assumed to be 15% with higher certainty (equivalent to data from 100 subjects).

Baseline demographic variables were summarized by randomization arm using means and SDs or medians and ranges (for continuous variables) or frequencies and percentages (for categorical variables), as appropriate. The primary analysis compared randomization arms with respect to POD 5 discharge using Fisher's exact test. Differences among treatment groups with respect to secondary continuous outcomes (postoperative median LOS, cost) were assessed using Wilcoxon rank-sum tests. Differences in binary outcomes (eg readmission rate, postoperative complications, DGE, anastomotic leaks, intra-abdominal abscesses, wound infection, urinary tract infection) were assessed using Fisher's exact test. Clinical data were analyzed quarterly as an oversight function by the Data Safety Monitoring Board.

RESULTS

Characteristics of the patients

From June 2015 to September 2017, 277 patients were screened for eligibility during preoperative surgical consultation. Sixty-eight patients did not consent to participate (Fig. 2). Among the remaining 209 patients who consented, 132 patients were not randomized due to predefined exclusion criteria (Fig. 2). A total of 77 patients were randomized, with 37 allocated to the WARP arm and 40 to the control arm. One patient randomized to the control arm withdrew consent after randomization

Table 1. Patient Demographics and Clinical Parameters

Clinical characteristic	WARP (n = 37)	Control (n = 39)
Female sex, n (%)	17 (45.9)	21 (53.8)
Age, y, median ± SD	65.8 ± 9.6	65.0 ± 9.3
BMI, kg/m^2, median ± SD	26.8 ± 4.3	26.1 ± 4.9
Diabetes mellitus, n (%)	11 (29.7)	10 (25.6)
History of tobacco use, n (%)	15 (40.5)	13 (33.3)
Median preoperative hemoglobin A1c, n (minimum, maximum)	6 (4.4, 9.7)	6 (4.4, 9.9)
Median preoperative albumin, n (minimum, maximum)	4.2 (3.3, 4.9)	4.1 (3.2, 4.5)
American Association of Anesthesiologists Class 3, n (%)	23 (62.1)	20 (51.3)
Neoadjuvant chemotherapy or chemoradiation, n (%)	4 (10.8)	7 (17.9)
Pathology, n (%)		
Periampullary adenocarcinoma	29 (78.4)	32 (82.1)
Pancreatic cystic neoplasm	3 (8.1)	3 (7.7)
Chronic pancreatitis	3 (8.1)	3 (7.7)
Other	2 (5.4)	1 (2.6)

WARP, Whipple accelerated recovery pathway.

and was therefore excluded, leaving 37 and 39 patients for analysis in the WARP and control groups, respectively.

Demographics, baseline clinical parameters, and operative variables were similar between the 2 groups (Table 1). The majority of patients in each group underwent pylorus-preserving PD (WARP 86.5%; control 82.1%) with the most common pathology being periampullary adenocarcinoma in both groups (WARP 78.4%; control 82.1%) (Table 1). Median estimated blood loss ($p = 0.94$) and operative time ($p = 0.82$) were also similar between the groups (Table 2).

Study outcomes

Collectively, there were fewer postoperative complications in the WARP group (29.7% vs 43.6%; $p = 0.24$) primarily as a result of a lower rate of DGE (13.5% vs 33%; $p = 0.059$), although the differences did not reach statistical significance (Table 2). The rates of pancreatic fistula, intra-abdominal abscess, urinary tract infection, as well as cardiac, renal, and pulmonary complications, were similar between the WARP and control groups (Table 2). Five patients (13.5%) randomized to the WARP arm required nasogastric tube reinsertion compared with 16 (41.0%) patients in the control arm ($p = 0.01$). Rates of other postoperative interventions, including antibiotic use, total parenteral nutrition, esophagogastroduodenoscopy, interventional radiology drain insertion, and transfer back to the surgical ICU were similar between the 2 groups (Table 2).

The interim analysis for efficacy was completed with data from 70 patients out of a planned accrual of 142 patients (Table 3). In the WARP group, the rate of POD 5 discharge was 74.3% (26 of 35) vs 14.3% (5 of 35) in the control arm ($p < 0.001$). The primary efficacy end point had been met, and the trial was halted by the Data Safety Monitoring Board.

While the interim analysis was being completed, 6 additional patients were enrolled. In the final analysis, 28 of 37 (75.7%) patients were discharged by POD 5 in the WARP group compared with 5 of 39 (12.8%) in the control group ($p < 0.001$) with similar rates of hospital readmission between groups (WARP 8.1%; control 10.3%; $p = 1.0$) (Table 3). The posterior probability that WARP increased the readmission rate by 5% over control was 3.9%. Among WARP patients, oral intake (solid and/or liquid) was significantly greater on POD 5 (1,120 mL vs 780 mL; $p < 0.001$), and inadequate oral intake prolonged the LOS beyond POD 5 in just 3 (8.1%) patients in the WARP group compared with 21 (53.8%) control patients ($p < 0.001$).

No deaths occurred within the first 30 or 60 postoperative days. Mortality analysis at 90 days revealed that 1 patient in the WARP group expired on POD 67 from an embolic CVA after multiple distant metastases developed from her underlying pancreas cancer. One month after operation, WARP patients experienced less weight loss (as a percentage of initial body weight: −5.5% vs −6.7%; $p = 0.021$) compared with control patients (Table 3). Among patients with periampullary malignancy, the median time to the initiation of adjuvant therapy was shorter in the WARP group (51 days vs 66 days; $p = 0.005$). Additionally, median hospital charges were significantly lower in the WARP group compared with the control group ($139,735 vs $155,542; $p = 0.006$).

Table 2. Perioperative Complications and Interventions

Complication	WARP (n = 37)	Control (n = 39)	p Value
EBL, mL, median (minimum, maximum)	200 (50, 600)	225 (50, 900)	0.94
Operative time, min, median (minimum, maximum)	385 (299, 479)	400 (290, 478)	0.82
Subject with ≥1 complication, n (%)	11 (29.7)	17 (43.6)	0.24
Total no. of complications, median (minimum, maximum)	0 (0,2)	0 (0,4)	0.14
Individual complication	—	—	—
Pancreatic fistula grade, n (%)	4 (10.8)	2 (5.2)	0.43
A	2 (5.4)	1 (2.6)	—
B	2 (5.4)	1 (2.6)	—
C	0 (0.0)	0 (0.0)	—
Delayed gastric emptying grade, n (%)	5 (13.5)	13 (33.0)	0.059
A	3 (8.1)	7 (17.9)	—
B	2 (5.4)	6 (15.4)	—
C	0 (0.0)	0 (0.0)	—
Intra-abdominal abscess, n (%)	1 (2.7)	1 (2.6)	1.0
Wound infection, n (%)	0 (0)	1 (2.6)	1.0
Urinary tract infection, n (%)	1 (2.7)	2 (5.2)	1.0
Cardiovascular, n (%)	1 (2.7)	0 (0)	0.49
Pulmonary, n (%)	0 (0.0)	3 (7.9)	0.24
Renal, n (%)	0 (0.0)	0 (0.0)	1.0
Deep vein thrombosis, n (%)	0 (0.0)	0 (0.0)	1.0
HJ/DJ leak, n (%)	0 (0.0)	0 (0.0)	1.0
Other, n (%)	0 (0.0)	2 (5.1)	0.49
Nasogastric tube reinsertion, n (%)	5 (13.5)	16 (41.0)	0.010
Postoperative antibiotic, n (%)	2 (5.4)	5 (12.8)	0.43
Total parenteral nutrition, n (%)	3 (8.1)	4 (10.3)	1.0
Esophagogastroduodenoscopy, n (%)	2 (5.4)	3 (7.7)	1.0
Interventional radiology drain, n (%)	2 (5.4)	1 (2.6)	0.61
Return to ICU, n (%)	0 (0)	1 (2.6)	1.0

EBL, estimated blood loss; HJ/DJ, hepaticojejunostomy/duodenojejunostomy; WARP, Whipple accelerated recovery pathway.

Likewise, the total cost (the direct plus indirect expense for individual patient charges) was reduced in the WARP group ($26,563 vs $31,845; p = 0.011) (Table 3).

DISCUSSION

Pancreatic cancer is currently the third leading cause of cancer death in the US.[22] By 2020, it is predicted to become the second leading cause of cancer death and to cost the US healthcare system $4.92 billion.[22,23] Surgical resection remains the only treatment option associated with prolonged survival and potential cure. We performed a randomized controlled clinical trial to evaluate whether an enhanced postoperative recovery pathway could decrease hospital LOS in patients undergoing PD. The WARP not only increased the number of patients discharged on POD 5 without affecting readmission rates, but it also expedited the initiation of adjuvant therapy and reduced hospital charges and cost. The WARP was associated with reduced rates of nasogastric tube re-insertion and trends toward lower rates of DGE and overall postoperative complications.

The safe reductions in LOS in the WARP group were likely a product of several interventions. First, patients and their families were notified of their anticipated discharge date on POD 0 and 1. The importance of managing patient expectations in achieving early discharge should not be understated,[24] as effective discharge communication and planning alone can empower patients to actively participate in their recovery and reduce hospital LOS.[25] Second, the WARP emphasized early mobilization and enhanced physical therapy, including an in-hospital gym visit. Few studies have evaluated the isolated impact of early mobilization after abdominal operation, but the adverse physiologic consequences of bed rest have been well-documented.[26] An earlier randomized trial from our institution documented the value of a

Table 3. Discharge and Recovery Outcomes

Outcome	WARP (n = 37)	Control (n = 39)	p Value
Length of stay, d, median (minimum, maximum)	5 (4, 11)	6 (5, 23)	<0.001
POD 5 discharge, n (%)	28 (75.7)	5 (12.8)	<0.001
POD 5 oral intake, mL, median (minimum, maximum)	1,120 (0, 2690)	780 (0, 1779)	<0.001
Inadequate dietary intake for discharge on POD 5, n (%)	3 (8.1)	21 (53.8)	<0.001
Readmission, n (%)	3 (8.1)	4 (10.3)	1.0
60-d mortality, n (%)	0 (0)	0 (0)	1.0
Percent change in body weight at 30-d follow-up, median (minimum, maximum)	−5.5 (−17.8, 3.7)	−6.7 (−16.7, 3.3)	0.021
Time to adjuvant therapy, d, median (minimum, maximum), n	51 (32, 84), 25	66 (40, 131), 30	0.005
Total hospital charges, US$, median (minimum, maximum)	139,735 (104,689, 253,830)	155,542 (125,519, 398,764)	0.006
Total cost, US$, median (minimum, maximum)	26,563 (20,988, 50,543)	31,845 (23,116, 88,858)	0.011

POD, postoperative day; WARP, Whipple accelerated recovery pathway.

post-PD exercise program in improving patient-reported outcomes, including quality of life.[27] Third, WARP patients had close telehealth follow-up after discharge with an experienced nurse practitioner with expertise in pancreas surgery recovery, a strategy effective in reducing medically unnecessary hospital readmission.[28]

In reviewing the data, the delay of oral intake until POD 3 appears to have been the intervention most crucial to enhanced recovery in the WARP group. Evidence supporting when and how patients should resume oral intake after PD has been scarce.[24] In general, ERAS protocols tend to advocate for an "early oral feeding" strategy,[10,24,29] a recommendation that was shown to be beneficial in a randomized trial that reported reduced morbidity and average hospital LOS from 16.7 days to 13.5 days with early, at-will oral feeding compared with enteral feeding in patients undergoing major upper gastrointestinal operations.[30] However, evidence supporting surgeon-initiated stepwise diet advancement (ie npo to liquid to solid) has been lacking.[24] In keeping patients npo for the initial 2 postoperative days and discharging them on a full liquid rather than a solid diet, WARP patients had greater intake on POD 5 and lower rates of DGE compared with control patients. Interestingly, WARP patients also experienced less postoperative weight loss during the month after operation. Pathophysiologically, post-PD DGE can be a consequence of a number of factors, such as peri-anastomotic edema delaying transit through the duodenojejunostomy, surgical disruption of enteric neural networks, postoperative ileus, and reductions in motilin levels that impair the synchrony of bowel motility.[31,32] We reasoned that a more conservative dietary advancement algorithm could allow for the resolution of generalized postoperative ileus, as well as the inflammation and tissue injury at the duodenojejunostomy before the initiation of significant oral intake.[33]

Aside from these interventions, the WARP is equally as notable for the streamlining of resources and avoidance of more complex and costly ERAS interventions that have been advocated for in other settings. For example, ERAS Society guidelines for pancreas surgery include the use of perioperative oral immune-nutrition to decrease infectious complications.[24] Similarly, to promote postoperative gut motility, others have promoted preoperative oral carbohydrate administration.[24] Minimizing opioid-induced suppression of gastrointestinal motility while maintaining adequate pain control has been another theorized strategy to accelerate surgical recovery and, despite the relative lack of evidence in pancreas-specific operations, thoracic epidural anesthesia, and IV nonopioid analgesics, such as lidocaine, are also being used increasingly to decrease systemic opioid use.[34-36] Similarly, the μ-opioid receptor antagonists methylnaltrexone and alvimopan have been used in an attempt to avoid the common opioid side effects on gut motility.[37] Others have proposed minimally invasive laparoscopic or robotic PD as a strategy to decrease bowel manipulation and hospital LOS.[38,39] With the WARP, despite having undergone open PD using patient-controlled analgesia with standard opioids (morphine/hydromorphone) and without preoperative immunonutrition, carbohydrate loading, or perioperative epidural anesthesia, median LOS in the WARP group was among the lowest reported for any cohort of patients undergoing PD.

This randomized trial has several limitations, including a single-center design, and lack of blinding that could introduce investigator bias. Although the primary end point of POD 5 discharge was met at the 50% accrual time point, the study was underpowered to make definitive conclusions about complication rates. We also acknowledge the stringent nature of the eligibility criteria and its limits on the trial's generalizability to a higher-risk patient cohort. Discharge by POD 5 after PD is radically below the national median,[40] and these criteria were conceived to ensure safety. These data appear applicable to high-performing PD patients at low risk of complications and suggest that if these patients are recovering well from operations, hospitalization beyond POD 5 is unnecessary. Importantly, this study was conducted in a high-volume center with an experienced surgical and perioperative management team, which might affect the generalizability of the findings. It is still unclear whether rigorous physical therapy is tolerable or whether the conservative WARP dietary algorithm can provide adequate nutrition to the cohort of patients with poor performance status or major medical comorbidities.[41] Among patients with normal, soft pancreas gland texture, morbidity rates tend to be higher, and so it is not entirely clear how such a factor could affect earlier hospital discharge.[42] The WARP proved remarkably safe and effective in the cohort of patients in this study, advocating for its cautious evaluation in other institutions and perhaps in a higher-risk PD patient population.

CONCLUSIONS

In summary, the WARP effectively facilitated recovery after PD in patients at low-to-moderate risk of postoperative complications. Hospital LOS, postoperative weight loss, the time to commencement of adjuvant therapy, as well as hospital charges and cost were all reduced by the WARP.

Author Contributions

Study conception and design: Lavu, Winter, Burkhart, Pucci, CJ Yeo

Acquisition of data: Lavu, McCall, TP Yeo, Cannaday

Analysis and interpretation of data: Lavu, McCall, Winter, Leiby, TP Yeo, Cannaday, CJ Yeo

Drafting of manuscript: Lavu, McCall, Winter, Burkhart, Pucci, Leiby, TP Yeo, Cannaday, CJ Yeo

Critical revision: Lavu, McCall, Winter, Burkhart, Pucci, Leiby, TP Yeo, Cannaday, CJ Yeo

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Discussion

DR DAVID B ADAMS (Charleston, SC): In a reminiscence study published in 1963, Allen O Whipple recounts how the correct procedure for pancreaticoduodenectomy took him 6 years to develop. The scientific method he used continued to be embraced by surgeons in their daily practice—that of trial and error. In his narrative account, Whipple describes the blind alleys he followed in developing the Whipple technique. He took one pathway and wrote, "That was a mistake." And then he took another pathway and he wrote, "That was a mistake." He finally found a third pathway, which he took, and he wrote, "That was a serious mistake." This reminds us that in surgical progress, failure happens a lot. You occasionally get lucky, and patience is a requirement.

Standardized, multidisciplinary, validated care pathways have replaced historic trial-and-error practice in the world of perioperative surgical care. Dr Lavu and his colleagues observed that many Whipple patients could be safely discharged on postoperative day 5. Rather than just doing an accelerated discharge pathway in a trial-and-error fashion, the authors undertook a randomized controlled trial comparing a 5-day recovery pathway to their standard protocol. By clearly defining a low-risk patient cohort, hospital length of stay was shortened without increasing readmission rates.

Did both groups get the same preoperative care? Are the advantages in the Whipple Accelerated Recovery Pathway (WARP) the delay in oral intake, fluid restriction, early mobilization, enhanced physical therapy, and telehealth follow-up alone? Is that all you need to do to decrease length of stay by 2 days and cut costs? What are the additional costs to the WARP? Is it the gym, the added physical therapist time, telehealth? Why did you stop the study early? There was no harm to patients in either arm of the study, and you may have achieved sufficient power to show