A retrospective study from a single center of 252 patients who underwent elective pancreaticoduodenectomy to compare perioperative hemodynamic optimization therapy and usual protocols in terms of perioperative cardiac function

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Abstract. Perioperative hemodynamic optimization therapy is used to improve cardiac function to meet the increased demand during the perioperative period and to reduce hypervolemia or hypovolemia, tissue hypoperfusion and other postoperative complications. The present single center retrospective study aimed to compare perioperative hemodynamic optimization therapy and usual protocols in terms of perioperative cardiac function in 252 patients who underwent elective pancreaticoduodenectomy. Patients underwent elective pancreaticoduodenectomy under usual protocols of enhanced recovery after surgery procedures without intraoperative fluid optimization (UC; n=142) or with intraoperative fluid optimization (FO; n=110). For intraoperative fluid and vasoactive medication optimization, the patients of the UG cohort underwent usual cardiovascular monitoring and in the FO cohort, fluid interventions were given if stroke volume variations were >20% during and at the end of surgeries. The length of the hospital stay (discharge from operation theater to discharge from the ward) of the FO cohort was shorter than that of the UC cohort (11.02±2.07 days vs. 14.95±3.97 days; P<0.0001). The fluid balance (total input fluid-total output fluid) was higher in the UC cohort than that in the FO cohort (6,101±695 ml vs. 4,623±358 ml; P<0.0001). The number of patients that required intraoperatively metaraminol was greater in the UC cohort than in the FO cohort (P<0.0001). The number of patients that required intraoperatively noradrenaline (P<0.0001) and dopamine/dobutamine (P<0.0001) administration was greater in the FO cohort than those in the UC cohort. A greater number of patients in the UC cohort suffered from pancreatic fistula, arrhythmia, postoperative delirium, electrolyte disturbances, hyponatremia, refractory analgesia and required intraoperative blood products (P<0.05 vs. FO cohort). Pancreaticoduodenectomy under usual protocol with intraoperative fluid optimization may have perioperative and postoperative benefits (level of evidence, 3; technical efficacy stage, 1).

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Introduction

There is an increase in incidences of pancreatic cancers worldwide (1). For periampullary malignancies, the mortality rate is 17-50% (2). Pancreaticoduodenectomy is the primary treatment strategy for periampullary malignancies including pancreatic adenocarcinoma and the other benign situations (1). However, pancreaticoduodenectomy is the cornerstone treatment for periampullary malignancies (2). The operative procedure is complex. Patents require a long recovery time and are often exposed to peri-operative complications (3).

Perioperative hemodynamic optimization therapy is used to improve cardiac function to meet the increased demand during the perioperative period and to reduce hypervolemia or hypovolemia, tissue hypoperfusion and other postoperative complications (4). Chloride-liberal fluid administration is common practice after pancreaticoduodenectomy (5). Inappropriate perioperative resuscitation during major abdominal surgeries and tissue hypoperfusion and/or edema for pancreaticoduodenectomy is associated with the development of postoperative complications (2,3,5,6). Enhanced recoveries after surgical procedures for patients undergoing pancreaticoduodenectomy have advocated a more equitable use of intravenous fluid administration (7,8). The management of carcinoma of the head of the pancreas by pancreatoduodenectomy, also known as Whipple procedure, as well as some current guidelines (9), such as the enhanced recovery after surgery recommendations, are focused on hypothermia, wound catheters, antimicrobial treatment and thromboprophylaxis therapies (9). Enhanced recovery after surgery procedures decreases the length of hospital stay for patients who underwent pancreaticoduodenectomy without

adverse effects on readmission and perioperative morbidity and mortality (9). By contrast, this protocol has no recommendations for fluid administration optimization (5,6). A multicenter randomized controlled trial (3) reported that perioperative precise fluid administration during pancreaticoduodenectomy can reduce the rate of complications after surgeries and length of hospital stay. However, this study was performed on a small sample size. Also, the optimal nutritional therapy is debatable for pancreaticoduodenectomy (10).

The present single center retrospective study aimed to compare perioperative hemodynamic optimization therapy and usual protocols in terms of perioperative cardiac function for 252 patients who underwent elective pancreaticoduodenectomy.

Materials and methods

Inclusion criteria. Patients (age >18 years old) with periampullary malignancies including pancreatic adenocarcinoma and the other benign situations who underwent elective pancreaticoduodenectomy were included in the analysis.

Exclusion criteria. Patients with preoperative coagulopathy, female patients with pregnancies, renal impairment (creatinine >250 μM/l), American Society Anesthesiology physical status >IV and chronic liver disease (as per Child-Pugh classification), patients who underwent distal, central, or total pancreatectomy and pancreatic enucleation were excluded from the study.

Cohorts. A total of 142 patients underwent elective pancreaticoduodenectomy under usual protocol of enhanced recovery after surgery procedures (UC cohort) and 110 patients underwent elective pancreaticoduodenectomy under protocols of enhanced recovery after surgical procedures with intraoperative fluid optimization (FO cohort).

Usual protocols of enhanced recovery after surgery procedures. Patients took no solids in the 6 h prior to surgery and no liquids in the 2 h prior to surgery . No intravenous fluid was administrated before anesthesia. Intrathecal 300-400 μg morphine (Duramorph; Hikma Pharmaceuticals USA, Inc.) analgesia was inserted at a lumbar spinal level before anesthesia. In cases of morphine allergies, patients received epidural analgesia inserted at a $T_{8/9}$ or $T_{9/10}$ level. A total of 3 mg/kg intravenous propofol (Diprivan®; Fresenius Kabi USA LLC), 1-3 μg/kg intravenous fentanyl (Novaplus; Hospira, Inc.) and 1 mg/kg intravenous bolus succinylcholine (Anectine; Sandoz, Inc.) injection were administered to induce anesthesia. Intraoperatively patients received 8 mg intravenous dexamethasone (APP Pharmaceuticals, LLC), 40 mg subcutaneous enoxaparin (Lovenox®; Sanofi Aventis) and 1 g intravenous paracetamol (B. Braun). In addition, 1 g intravenous ceftriaxone (Rocephin; Pfizer, Inc.), 1 g intravenous ampicillin (Pfizer Inc.) and 500 mg intravenous metronidazole (Pfizer Inc.) were administered as prophylaxis. Continuous electrocardiography, capnography, pulse oximetry, central venous pressure, blood pressure, pulse pressure variations, body temperature and urine output were recorded intraoperatively. Sevoflurane (Piramal Critical Care, Inc.) with air and oxygen (50:50) mixture was used to maintain bispectral index 40-60. A total of 0.1-0.3 μg/kg/min intravenous remifentanil (Ultiva®; Mylan Institutional LLC) was started after administration of anesthesia and discontinued after the closure of the wound. Epidural analgesia was given with 10 ml 0.2% ropivacaine (Novartis International AG) using an epidural catheter 30 min prior to wound closure. This epidural anesthesia was followed by 10 ml/h epidural infusion. Subsequently, patients received 3 μg/kg of intravenous fentanyl (3). All interventions were administered by anesthesiologists (minimum 3-years' experience) at the institutes.

Intraoperative fluid and vasoactive medication optimization. Blood pressure was measured using an arterial line catheter (20G; Vygon (UK), Ltd.) before anesthesia. A central venous catheter [Vygon (UK), Ltd.] was used to record central venous pressure. The FloTrac™ pulse contour device (Vigileo™, Edwards Lifesciences) was connected to a hemodynamic monitor (Philips Healthcare) and arterial line catheter. The arterial line pressure bag using the sensor stopcock was maintained at 300 mmHg. Patients of the UG cohort underwent usual cardiovascular monitoring by anesthesiologists for intraoperative fluid and vasoactive medication optimization. Patients of the FO cohort followed protocol (Fig. 1) for intraoperative fluid and vasoactive medication optimization. In the FO cohort, fluid interventions were given if stroke volume variations were >20% during and at the end of surgeries (3).

High cardiac index. Cardiac index >2 l/min/m^2 was considered a high cardiac index.

Outcomes measures.

Postsurgical management. After operations, all patients were admitted to postoperative intensive care units (PICU) for 1 day and then transfer to the ward. All patients received 0.05-0.1 mg/kg/h of ketamine (Ketalar®; Pfizer Inc.) infusion in PICU for 1 day. A total of 20 μg twice a day of bolus fentanyl (5 min lockout) was given to patients until they could take a solid diet. After initiation of solid intake, patients received 10-20 mg of oral oxycodone (OxyContin; Purdue Pharma L.P.) every 4 h. Epidural anesthesia was locked after 2-3 days from the operation. All patients received 1 g intravenous paracetamol four times a day for 2 days and 40 mg intravenous pantoprazole (Protonix®, Pfizer Inc.) once a day for 1 week after surgeries. Rescue analgesia included 30 mg/8 h intravenous ketorolac (Athemex Pharmaceuticals) or 50-100 mg/6 h intravenous tramadol (Ultram; ProCare). Prophylaxis antibiotics were continued for 1 day after the operation and physiotherapies were delivered twice daily after operations. Nasogastric tubes (Roche Diagnostics) were removed after the operation if less than 300 ml of drainage was reported within 6 h. After surgery, a liquid diet was started and a solid diet was started 2 days after surgery. The surgical drains were removed if there were no pancreatic or biliary leakage. Pancreatic enzyme supplements (Doctor' Best, Inc.) were given when the soft diet was started. Strict serum glucose control (target: 6-10 mM/l) was maintained using an insulin sliding scale. A urinary catheter was removed 3 days after the surgeries. A total of 200 mg/12 h docusate sodium (Perrigo Co.) was given 4 days after surgeries for regular bowel motions (3). After surgeries, patients were managed by surgeons (who performed surgeries; minimum

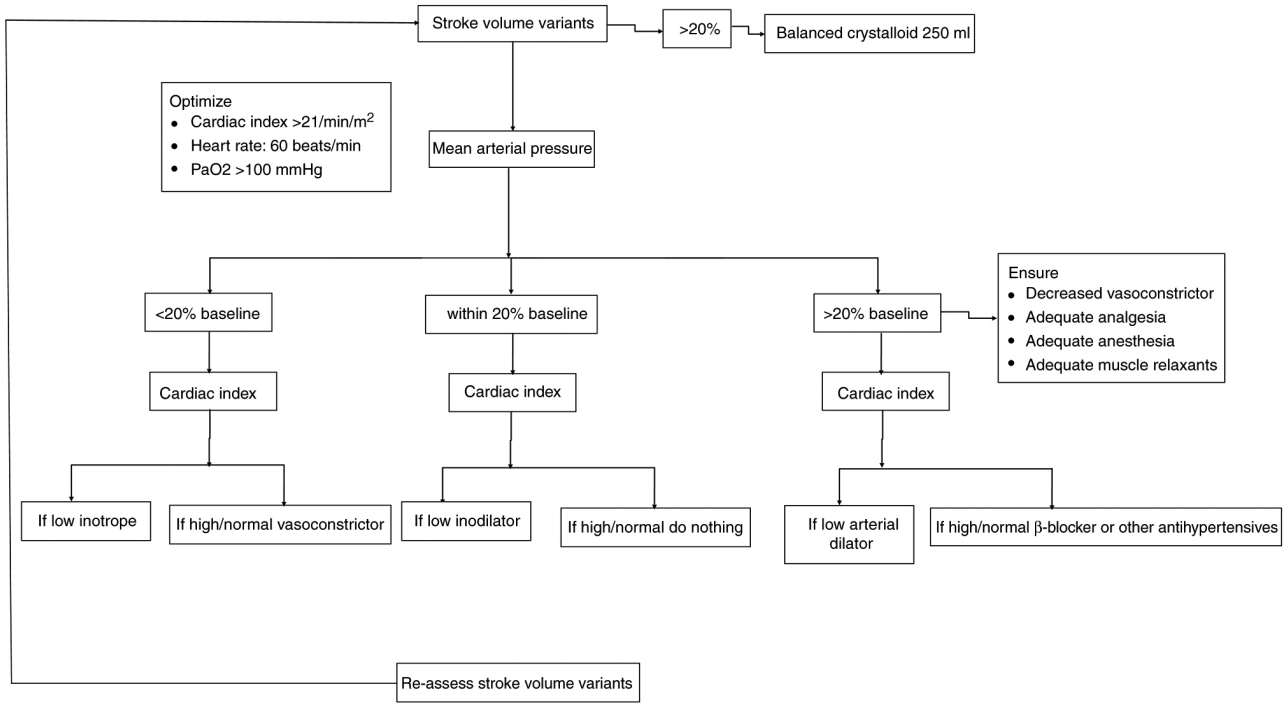

Figure 1. Protocol of intraoperative fluid and vasoactive medication optimization. PaO_2: The partial pressure of oxygen.

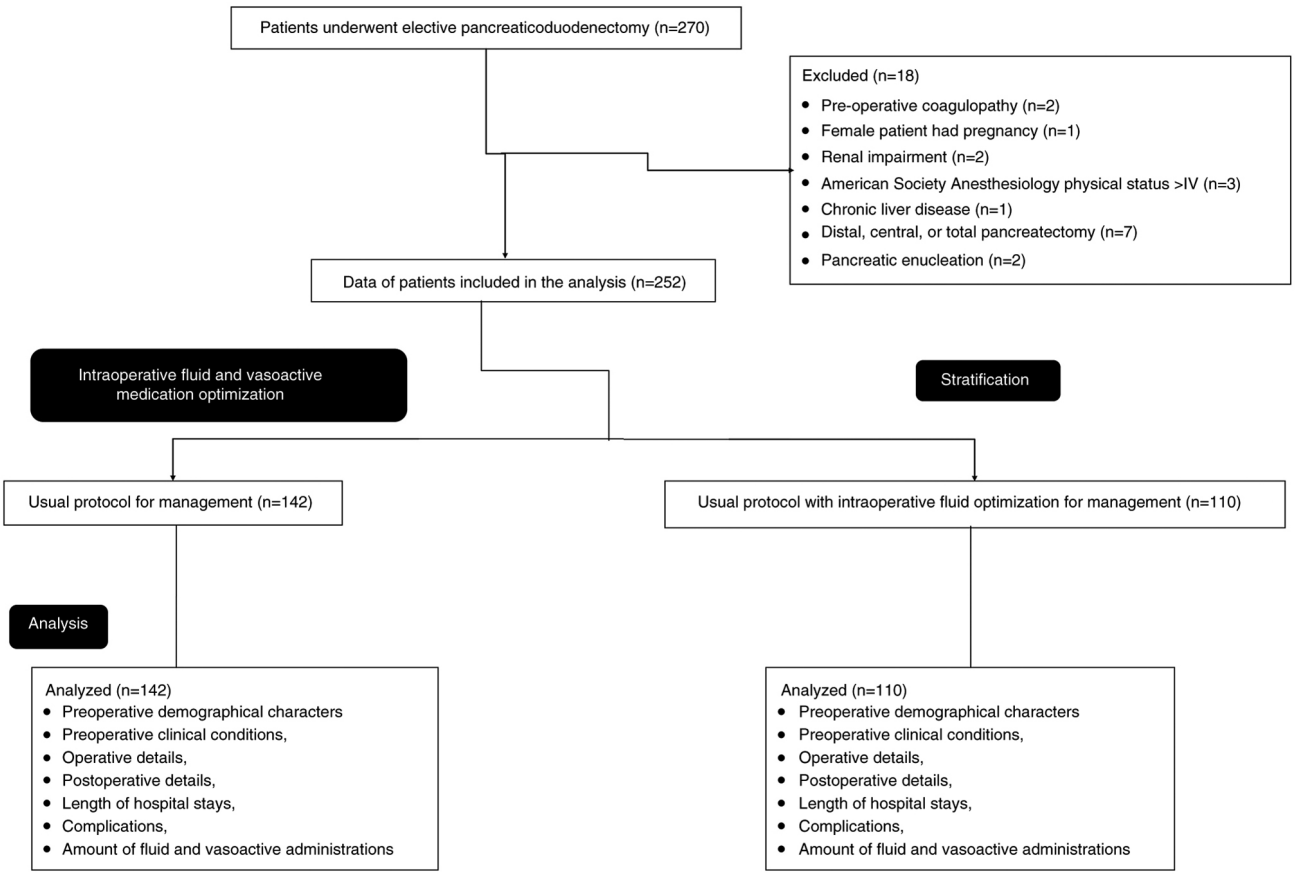

Figure 2. Flow diagram of the present study.

3-years of experience) and physicians (minimum 3-years of experience; unaware of intraoperative fluid and vasoactive medication optimization protocol) of the institutes in PICU and ward.

Table I. Preoperative demographical characters, preoperative clinical conditions and operative variables of the enrolled patients.

Parameters	Cohorts		Comparisons between cohorts, P-value
	UC	FO	
Numbers of patients who underwent pancreaticoduodenectomy	142	110	
Age, years			0.303
Range	52-74	52-75	
Mean ± SD	62.15±7.15	63.21±9.15	
Sex			0.701
Male	85 (60)	63 (57)	
Female	57 (40)	47 (43)	
Body mass index, kg/m^2			0.101
Range	21-29	21-29	
Mean ± SD	24.95±1.85	25.33±1.77	
Ethnicity			0.935
Han Chinese	130 (92)	101 (92)	
Mongolian	10 (7)	8 (7)	
Tibetan	2 (1)	1 (1)	
Comorbidities			0.602
Diabetes	45 (32)	39 (35)	
Chronic obstructive pulmonary diseases	8 (6)	2 (2)	
Hypertension	21 (15)	20 (18)	
Peripheral vascular disease	2 (1)	1 (1)	
Malignancy	111 (78)	101 (92)	
Ischemic heart disease	4 (3)	2 (2)	
Blood chemistry			
Hemoglobin, mg/dl			0.106
Range	129-147	126-143	
Mean ± SD	13.35±0.75	13.51±0.81	
White blood cell count, $x10^9/l$			0.063
Range	5.65-8.55	5.75-9.05	
Mean ± SD	7.15±0.14	7.19±0.20	
Platelets, $x10^9/l$			0.071
Range	180-290	178-289	
Mean ± SD	230±13	227±13	
Albumin, g/l			0.088
Range	36-46	32-42	
Mean ± SD	39±5	38±4	
Creatinine, $\mu M/l$			0.115
Range	58-87	60-95	
Mean ± SD	68±4	69±6	
Bilirubin, $\mu M/l$			0.075
Range	7-14	8-18	
Mean ± SD	9±3	8.4±2.1	
Urea, $\mu M/l$			0.064
Range	4.2-6.8	4.6-7.7	
Mean ± SD	5.85±0.85	6.08±1.11	
Glomerular filtration rate, $ml/min/1.73\ m^2$			0.079
Range	81-91	78-92	
Mean ± SD	85±4	84±5	
American Society Anesthesiology physical status			0.852
I-II	45 (32)	31 (28)	
III-IV	97 (68)	79 (72)	

Table I. Continued.

Parameters	Cohorts		Comparisons between cohorts, P-value
	UC	FO	
Anesthesia method			0.224
Morphine	115(81)	82(75)	
Epidural anesthesia	27(19)	28(25)	
Duration of surgery, h			0.103
Range	7.21-9.65	7.11-9.55	
Mean ± SD	8.55±0.42	8.45±0.55	

Categorial and ordinal variables are presented as frequency (percentages) and continuous variables are presented as mean ± SD. Fisher exact test or the chi-square test of independence was used for categorical and ordinal variables and an unpaired t-test was used for continuous variables for statistical analysis. All results were considered significant if P<0.05. Degree of freedom: 250 when applicable. SD, standard deviation. FO, elective pancreaticoduodenectomy performed under protocols of enhanced recovery after surgical procedures with intraoperative fluid optimization; UC, elective pancreaticoduodenectomy under usual protocols of enhanced recovery after surgery procedures without intraoperative fluid optimization.

Preoperative demographical characters and clinical conditions of patients, operative details and postoperative details were retrospectively collected from patients' records of institutes. Fluid balance was calculated as per Eq. 1 (3):

(1) Fluid balance = Total input fluid - Total output fluid

Were Total input fluid = Intravenous fluid administration + parenteral medication + water from feeding + oral water intake. Total output fluid = Blood loss + urine output + fluid loss from drains + vomiting.

Length of hospital stay. Patients that showed unassisted mobilization, normal eating and drinking without nausea, defecation, satisfactory oral analgesia, no evidence of complications or particularly infection(s) were discharged from the hospital (3). The length of hospital stay was defined as discharge from operation theater to discharge from the ward.

Amount of fluid and vasoactive administrations. Data regarding fluid administrations and vasoactive medications were retrospectively collected from medical records of patients of institutes.

Complications. The unexpected events that occurred after discharge from the operation theater to discharge from the ward were considered complications. The Clavien-Dindo Classification (11) was used to grade complications. The Clavien-Dindo Classification was graded as: i) I, deviation from the normal postoperative condition that did not require pharmacological or surgical treatment; ii) II, deviation required pharmacological treatment; iii) IIIa, deviation required endoscopic, radiation, or surgical interventions and did not require general anesthesia; iv) IIIb, deviation required endoscopic, radiation, or surgical interventions and required general anesthesia; v) IVa, single organ life-threatening dysfunctions; vi) IVb, multiple organ life-threatening dysfunctions; and vii) V, death (12). The International Study Group of Pancreatic Surgery was used to grade and classify pancreatic leaks and delayed gastric emptying (13). According to requirements for repairing, the postoperative pancreatic fistula was graded as: i) A, required minor adjustments; ii) B, required significant changes from the normal clinical route; and iii) C, required major invasive procedures (13). A statement from the European Society of Anesthesiology and the European Society of Intensive Care Medicine joint task force for the European

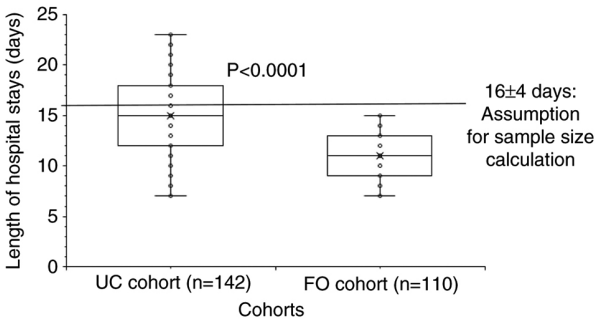

Figure 3. Hospital stays of patients. The length of hospital stay was defined as discharge from operation theater to discharge from the ward.

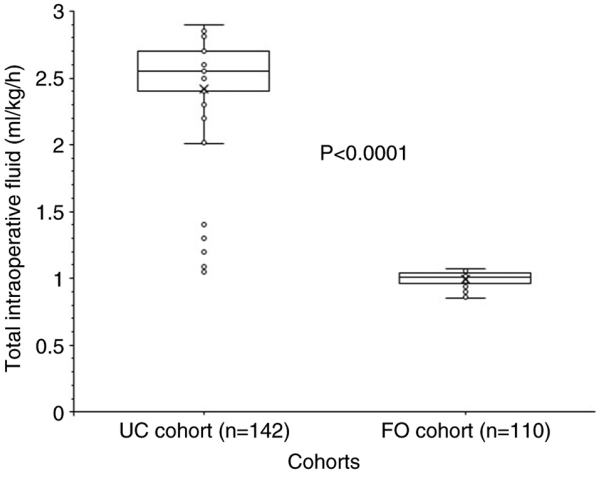

Figure 4. Intraoperative fluid rate.

Table II. Fluid administration during hospital stays.

Parameters	Cohorts		Comparisons between cohorts, P-value
	UC	FO	
Numbers of patients who underwent pancreaticoduodenectomy	142	110	
Intravenous fluid administration, ml			
Crystalloid			<0.0001
Range	6,000-8,000	4,000-7,600	
Mean ± SD	8,218±964[a]	6,297±846	
Colloid			<0.0001
Range	0-550	0-550	
Mean ± SD	146±128[a]	279±169	
Blood products			0.033
Range	0-250	0-250	
Mean ± SD	40±92[a]	18±65	
Parenteral medication, ml			0.445
Range	950-1,100	950-1,100	
Mean ± SD	1,009±42	1,005±43	
Water from feeding + oral water intake, ml			0.071
Range	2,800-3,100	2,800-3,100	
Mean ± SD	2,969±86	2,950±74	
Total input fluid, ml			<0.0001
Range	10,050-14,400	8,050-11,850	
Mean ± SD	12,382±945[a]	10,549±868	
Urine output, ml			<0.0001
Range	5,000-6,700	3,950-6,500	
Mean ± SD	5,620±226[a]	5,345±601	
Blood loss, ml			0.036
Range	100-550	50-300	
Mean ± SD	206±114[a]	233±79	
Fluid loss from drains, ml			<0.0001
Range	250-600	250-400	
Mean ± SD	446±85[a]	336±59	
Vomiting, ml			0.221
Range	0-100	0-100	
Mean ± SD	8±24	12±30	
Total output fluid, ml			<0.0001
Range	5,350-7,000	4,250-7,200	
Mean ± SD	6,281±355[a]	5,926±676	

Variables are presented as mean ± SD. An unpaired t-test was used for statistical analysis. All results were considered significant if $P<0.05$. [a]Statistically higher than FO cohort. Degree of freedom: 250. SD, Standard deviation. FO, elective pancreaticoduodenectomy performed under protocols of enhanced recovery after surgical procedures with intraoperative fluid optimization; UC, elective pancreaticoduodenectomy under usual protocols of enhanced recovery after surgery procedures without intraoperative fluid optimization.

Perioperative Clinical Outcome was used to define the other perioperative complications (14).

Statistical analysis. The study assumed that the length of the hospital stay of patients would have been 16±4 days (3). The sample size was calculated based on the length of the hospital stay of patients, 80% power calculation ($\beta=0.2$) and two-sided type-I error of 0.05% ($\alpha=0.05$) at a 95% of confidence level. The sample size (minimum number of patients required in each cohort) was 105. InStat 3.01 (GraphPad Software, Inc.) was used for statistical analysis. Categorial and ordinal variables are presented as frequency (percentages) and continuous

variables are presented as mean ± standard deviation. Fisher exact test or the Chi-square test (χ^2-test) of independence was used for categorical and ordinal variables. Distribution of continuous data checked whether they are distrusted normal or not normal visually through frequency distribution. For the normal distribution of data of continuous variables, an unpaired t-test was used for statistical analysis. For the not normal distribution of data of continuous variables, the Mann-Whitney test was used for statistical analysis. The variance homogeneity of normally distributed continuous data has been checked using the Brown- Forsythe test. If population variance is not equal unpaired t-test with Welch correction was used for continuous data and if population variance is equal unpaired t-test was used for continuous data. All results were considered significant at a 95% confidence interval of the difference (Cl).

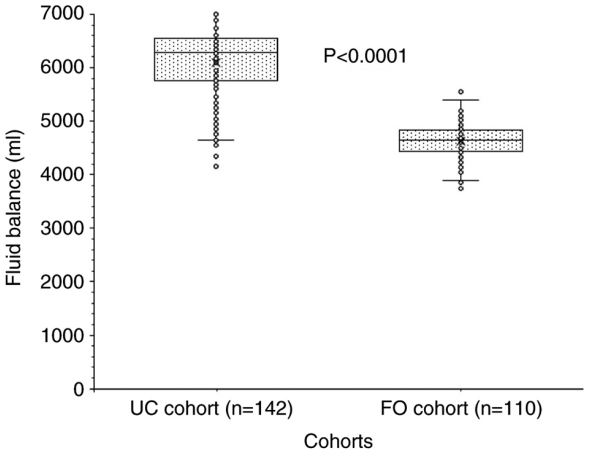

Figure 5. Fluid balance during hospital stays. Fluid balance: Total input fluid (ml)-total output fluid (ml).

Results

Study population. From 15 May 2018 to 21 May 2020, a total of 270 patients underwent elective pancreaticoduodenectomy at the department of gastroenterology of the parent hospital and the referring hospitals. Among them, two patients have preoperative coagulopathy, one female patient had a pregnancy, two patients had renal impairment, three patients had the American Society Anesthesiology physical status >IV, one patient had chronic liver disease and seven patients underwent distal, central, or total pancreatectomy and two patients had pancreatic enucleation. Therefore, data of these patients (n=18) were excluded from the analysis. Data of preoperative demographical characteristics and clinical conditions, operative and postoperative details, as well as length of hospital stay, complications, amount of fluid and vasoactive administrations of a total of 252 patients were retrospectively collected from hospital records after having received written approval from authorities and analyzed. The flow chart of the study is reported in Fig. 2.

Demographical characters, comorbidities, blood chemistry and operative variables. Cancer was the most common reason for pancreaticoduodenectomy. There were no significant differences between preoperative demographical characters, ethnicity, preoperative comorbidities, preoperative blood chemistry, preoperative glomerular filtration rate and operative variables of the enrolled patients (Table I; Fisher's exact test/χ^2-test and parametric/ nonparametric test; P>0.05 for all parameters).

Length of hospital stays. The length of hospital stay for patients in the FO cohort was shorter than that of patients in the UC cohort [11.02±2.07 days (range, 7-10 days) vs. 14.95±3.97 days (range: 7-23 days); P<0.0001; degree of freedom (df): 250; 95% CI: -4.752 to -3.113; t-test; Fig. 3).

Fluid administration during hospital stays. Total intraoperative fluid was given at rate of 0.99±0.05 ml/kg/h (range, 0.85-1.01 ml/kg/h) for patients in the FO cohort and at rate of 2.42±0.4 ml/kg/h (range, 1.05-2.9 ml/kg/h) for patients in the UC cohort. Intraoperative fluid administration rate was higher for patients of the UC cohort than the FO cohort (P<0.0001, df: 147; 95% CI: -1.492 to -1.359; t-test with Welch correction; Fig. 4). Administration of blood products in the UC cohort was also higher than in the FO cohort (P=0.033). This result may be related to intraoperative bleeding and surgery time. Intraoperative bleeding was higher in the UC cohort than that in the FO cohort (P=0.036). The surgery time was higher in the UC cohort compared with that in the FO cohort; however, this was not statistically significant.

The amount of crystalloid fluid (P<0.0001) and blood products (P=0.033) administered were higher in the UC cohort than those in the FO cohort. Also, urine output was higher in the UC cohort than that in the FO cohort (P<0.0001). The postoperative input fluid was the similar in both cohorts (P>0.05 for all types of administrations). Total input fluid in the UC cohort was 1.17 times higher than that in the FO cohort. However, total output fluid in the UC cohort was only 1.06 times higher than that in the FO cohort. The details of fluid administration during hospital stays are reported in Table II. Fluid balances in the UC cohort were higher than those in the FO cohort (6,101±695 ml vs. 4,623±358 ml; P<0.0001; df: 220; 95% CI: -1611.6 to -1345.4; t-test with Welch correction; Fig. 5).

Intraoperative vasoactive medication. The number of patients in the UC cohort requiring intraoperatively metaraminol was higher than that in the FO cohort (P<0.0001; Fisher's test). However, the number of patients administered intraoperatively with noradrenaline (P<0.0001; Fisher's test) and dopamine/dobutamine (P<0.0001; Fisher's test) was higher in the FO cohort than that in the UC cohort. The details of intraoperative vasoactive medication are reported in Table III.

Complications. A total of 116 (82%) from the UC cohort and 81 (74%) of patients from the FO cohort reported complications (P=0.128; Fisher's test). The higher numbers of patients of the UC cohort were reported for grade A pancreatic fistula (P=0.011; Fisher's test), grade C pancreatic fistula (P=0.037; Fisher's test), all grades of pancreatic fistula (P=0.0001; Fisher's test), arrhythmia (P=0.026; Fisher's test), postoperative delirium (P=0.001; Fisher's test), electrolyte disturbances (P=0.028; Fisher's test), hyponatremia (P=0.046; Fisher's test), refractory analgesia (P=0.014; Fisher's test) and blood products

Table III. Intraoperative vasoactive medication.

Parameters	Cohorts		Comparisons between cohorts, P-value
	UC	FO	
Numbers of patients who underwent pancreaticoduodenectomy	142	110	
Any vasoactive drug	135 (95)	109 (99)	0.072
Noradrenaline	45 (32)	98 (89)[b]	<0.0001
Ephedrine	40 (28)	41 (37)	0.126
Metaraminol	110 (77)[a]	15 (14)	<0.0001
Dopamine/Dobutamine	7 (5)	40 (36)[b]	<0.0001
β-blockers	22 (15)	22 (20)	0.352

Variables are presented as frequency (percentages). Fisher's exact test was used for statistical analysis. All results were considered significant if P<0.05. [a]Higher numbers of patients than those of the FO cohort. [b]Higher numbers of patients than those of the UC cohort. FO, elective pancreaticoduodenectomy performed under protocols of enhanced recovery after surgical procedures with intraoperative fluid optimization; UC, elective pancreaticoduodenectomy under usual protocols of enhanced recovery after surgery procedures without intraoperative fluid optimization.

requirements (P=0.035; Fisher's test) than those of the FO cohort. The number of patients that reported drug reaction was greater in the FO cohort than that in the UC cohort (P=0.012; Fisher's test). The details of perioperative and postoperative complications are reported in Table IV.

The UC cohort reported 3.68 complications/patient, while the FO cohort reported 2.61 complications/patient. The patients who underwent pancreaticoduodenectomy under usual protocol reported higher numbers of perioperative and postoperative complications than those who underwent pancreaticoduodenectomy under usual protocol with intraoperative fluid optimization (P=0.024; df: 8, χ^2-test; Fig. 6). The number of patients with >4 complications in FO cohort was lower than that in the UC cohort [25 (23%) vs. 62 (44%); P=0.0005; Fisher's exact test].

Discussion

The present study indicated that patients who underwent pancreaticoduodenectomy under the usual protocol of enhanced recovery after surgical procedures with intraoperative fluid optimization had shorter hospital stay, lower intraoperative fluid rate, fewer fluid balance during hospital stay and fewer perioperative and postoperative complications than those who underwent pancreaticoduodenectomy under the usual protocol of enhanced recovery after surgical procedures. The results of the current study are in agreement with the results of a multicenter randomized controlled trial (3), retrospective analyses (2,5,6,15), whereas it is only partially in agreement with the results from a retrospective analysis (16) and a randomized trial (17). A clinical trial performed on the English population (3), retrospective analyses on the North American population (2,15) and the Australian population (5) have small sample sizes; notably, a small sample size may increase the risk of a type-I error. In addition, several retrospective studies (2,5,6,15) used old records of patients for chart reviews and data analyses. At the time of those trials several complications were not clearly understood, like the pancreatic leak which was not clearly understood until 2005 (6). Enhanced recovery after surgery procedures protocol (8) is implemented with specific guidelines (18,19). Pancreaticoduodenectomy under usual protocol with intraoperative fluid optimization may have perioperative and postoperative benefits.

The range of hospital stay of all patients was 7-23 days even though enhanced recovery after surgery procedures protocol (8) is implemented in the study. Total input fluid in the UC cohort was 1.17 times higher than that in the FO cohort. However, total output fluid in the UC cohort was only 1.06 times higher than that in the FO cohort. Postoperative input fluid was similar in the two cohorts. Thus, intraoperative fluid administration was higher in the UC cohort than in the FO cohort. Goal-directed fluid administration reduces hospital stays (20). The results of hospital stay, fluid administration and fluid output of the current study were in agreement with the results from a multicenter randomized controlled trial (3) and retrospective study (21). Pancreaticoduodenectomy under usual protocol with intraoperative fluid optimization improves the outcomes.

In the present study reported that the number of patients that suffered from pancreatic fistula, arrhythmia, postoperative delirium, electrolyte disturbances, hyponatremia, refractory analgesia and blood product requirements was higher in the UC cohort than in the FO cohort. The results of perioperative and postoperative complications of the current study concur with the study on elective cardiac surgery (22). Fluid liberal therapies can have requirements for the administration of blood products, such as blood and plasma transfusions (23), and administration of these blood products to patients can reduce survival after surgery (24). Perioperative fluid choice and therapies should be individualized (25) because body weight and body mass index are associated with perioperative and postoperative complications (10). A fluid liberal regimen is responsible for perioperative and postoperative complications.

Table IV. Perioperative and postoperative complications.

Parameters	Cohorts		Comparisons between cohorts, P-value
	UC	FO	
Numbers of patients who underwent pancreaticoduodenectomy	142	110	
Clavien-Dindo Classification			
I	18 (13)	12 (11)	0.699
II	25 (18)	15 (14)	0.487
IIIa	1 (1)	5 (4)	0.089
IIIb	1 (1)	5 (4)	0.089
Iva	4 (3)	1 (1)	0.391
IVb	1 (1)	1 (1)	0.999
V	0 (0)	0 (0)	N/A
Total	50 (35)	39 (35)	0.999
Wound infection	23 (16)	15 (14)	0.599
Superficial surgical site infection	21 (15)	15 (14)	0.857
Deep surgical site infection	11 (8)	5 (4)	0.436
Sepsis	17 (12)	9 (8)	0.406
Pancreatic fistula			
Grade A	21 (15)[a]	5 (4)	0.011
Grade B	11 (8)	4 (4)	0.192
Grade C	6 (4)[a]	0 (0)	0.037
Total	38 (27)[a]	9 (8)	0.0001
Delayed gastric emptying	21 (15)	10 (9)	0.183
Bile leak. the presence of bile in the drainage fluid that persisted on postoperative day 4	6 (4)	1 (1)	0.141
Cardiorespiratory complications	37 (26)	20 (18)	0.172
Acute respiratory distress syndrome	5 (4)	1 (1)	0.236
Pneumonia	7 (5)	5 (4)	0.998
Pulmonary atelectasis	11 (8)	4 (4)	0.192
Pulmonary congestion	11 (8)	8 (7)	0.998
Cardiogenic pulmonary edema	3 (2)	1 (1)	0.634
Arrhythmia	12 (8)[a]	2 (2)	0.026
Acute pancreatitis, serum lipase >50 U/dl	1 (1)	5 (4)	0.089
Gastrointestinal bleeding	7 (5)	1 (1)	0.143
Acute kidney injury	9 (6)	2 (2)	0.119
Postoperative delirium	21 (15)[a]	3 (3)	0.001
Ischemic hepatitis	7 (5)	1 (1)	0.143
Nausea	23 (16)	21 (19)	0.617
Vomiting	16 (11)	18 (16)	0.267
Electrolyte disturbances	31 (22)[a]	12 (11)	0.028
Hypokalemia	18 (13)	9 (8)	0.307
Hyponatremia	9 (6)[a]	1 (1)	0.046
Hypomagnesemia	7 (5)	5 (4)	0.998
Hypophosphatemia	7 (5)	1 (1)	0.143
Hyperkalemia	4 (3)	1 (1)	0.391
Hypernatremia	2 (2)	1 (1)	0.999
Endocrine abnormalities	3 (2)	2 (2)	0.634
Drug reaction	1 (1)	8 (7)[b]	0.012
Refractory analgesia	22 (15)[a]	5 (4)	0.014
Urinary tract infection	2 (2)	1 (1)	0.999
Fluid overload	3 (2)	1 (1)	0.634
Blood products requirements	23 (16)[a]	8 (7)	0.035

Table IV. Continued.

Parameters	Cohorts		Comparisons between cohorts, P-value
	UC	FO	
Return to operation theatre from postoperative intensive care units and/or ward	22 (15)	17 (15)	0.998
Return to postoperative intensive care units from the ward	13 (9)[a]	1 (1)	0.004
Number of complications	522	287	N/A
Patients with complications	116 (82)	81 (74)	0.128
Complications per patients	3.68	2.61	N/A

Variables are presented as frequency (percentages). Fisher's exact test was used for statistical analysis. All results were considered significant if $P<0.05$. [a]Higher numbers of patients than those of the FO cohort. [b]Higher numbers of patients than those of the UC cohort. N/A: Not applicable. FO, elective pancreaticoduodenectomy performed under protocols of enhanced recovery after surgical procedures with intraoperative fluid optimization; UC, elective pancreaticoduodenectomy under usual protocols of enhanced recovery after surgery procedures without intraoperative fluid optimization.

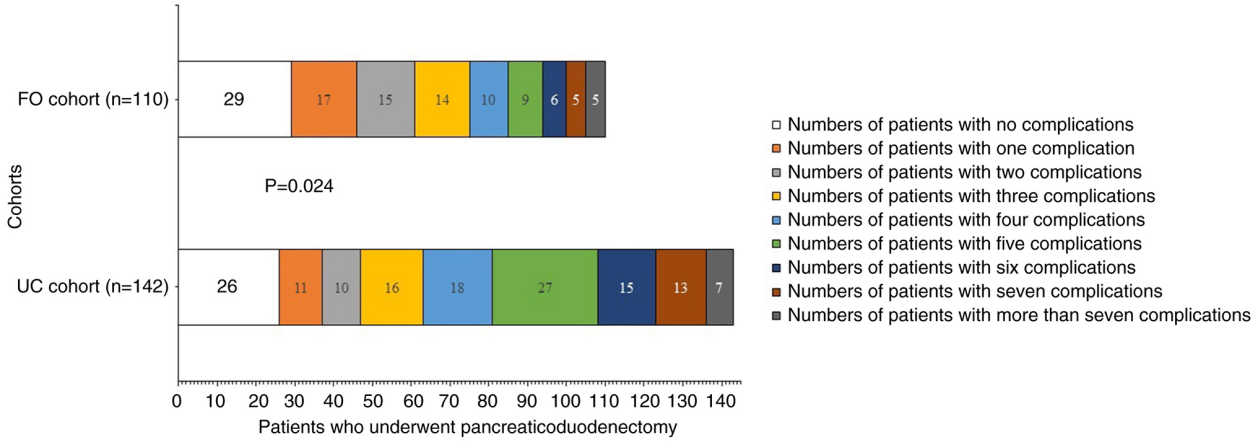

Figure 6. Details of patients with several complications. The unexpected events that occurred after discharge from the operation theater to discharge from the ward were considered complications.

The data of the current study also showed a lower percentage of patients with >4 complications in the FO cohort than in the UC cohort. The results of complications of the current study were not consistent with those of a multicenter randomized controlled trial (3). The small sample size of a multicenter randomized controlled trial (3) may be responsible for the contradictory results. The present results also demonstrated the advantage of a new practice of intraoperative fluid optimization in decreasing the number of complications.

A greater number of patients received noradrenaline and dopamine/dobutamine during pancreaticoduodenectomy under the usual protocol with intraoperative fluid optimization than during pancreaticoduodenectomy under the usual protocol. Noradrenaline and dopamine/dobutamine preserved plasma volume and compensated for the requirements for fluid administration (3). To the best of our knowledge, the effects of fluid administrations combined with adrenergic and/or vasoactive therapies have not been formally evaluated in human clinical trials. However, the experimental study reported that α1 agonists with vasoactive drugs can accelerate the distribution and the elimination of fluid, while β1 agonists can delay the distribution and the elimination of fluid (26). The low dose of phenylephrine administration can slow down the distribution of fluid from the plasma to the interstitial fluid space and decrease the risk of hypovolemia (27). However, volume expansions of fluid in conjugations with vasoactive medications are difficult to understand because of the confounding effects of anesthesia, surgery and clinical and pathological characteristics of patients (3). In addition to parenteral fluid administrations, the current study provides recommendations for intraoperative vasoactive medications.

In the current study, the patients in the FO cohort received fluid administration if stroke volume variations were >20% during and at the end of surgeries. The cut-off value of fluid interventions in the current study was the same as that of a multicenter randomized controlled trial (3) and a retrospective study (28). The stroke volume variations are inconclusive between 9 and 13% limits for 25% of patients under general

anesthesia (29,30). However, the previous randomized trials (31-33) on conventional fluid administration optimization protocols are less fluid restrictive than what was used in the surgeries of the current studies. The current study justified the cut-off value of fluid interventions.

The present study had several limitations. For example, it did not report data on the size of the pancreatic duct, the texture of the pancreas, the number of lymph nodes retrieved and the complexity of surgeries. However, the present study was focused on non-surgical factors and patient's outcomes. The sample size was calculated based on the hospital stay of patients, however it was not calculated for complications. The protocols are designed for pancreaticoduodenectomy and cannot be extrapolated to other cardiac, emergency and orthopedic surgeries. The present study is a non-randomized, single-center study and lacks dynamic study.

In conclusion, the findings of the current study indicated that patients who underwent pancreaticoduodenectomy under usual protocol with intraoperative fluid optimization had shorter hospital stay, fewer fluid balance during hospital stays, fewer perioperative and postoperative complications, as well as fewer requirements for intraoperative blood products than those who underwent pancreaticoduodenectomy under the usual protocol without intraoperative fluid optimization. Intraoperative fluid administration optimization with proper intraoperative vasoactive medications during pancreaticoduodenectomy decreases the risk of perioperative and postoperative complications.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

LL was the project administrator and contributed to supervision, validation, methodology and the literature review of the study. YW contributed to the investigation, methodology, conceptualization, software and literature review of the study. XN contributed to formal analysis, data curation, resources and the literature review of the study and drafted and edited the manuscript for intellectual content. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy. LL and YW confirm the authenticity of all the raw data. All authors read and approved the final version of manuscript.

Ethics approval and consent to participate

The designed protocol (approval no. DMUCL1520, dated 10 December 2020) was approved by the Dalian Medical University review board and the Chinese Society of Critical Care Medicine. The study reporting adheres to the law of China, the STROBE (the strengthening the reporting of observational studies in epidemiology) guidelines and the V2008 Declarations of Helsinki. Consent for participation in the present study was not required due to the retrospective nature of the study. Being a retrospective study the registration in the Chinese Clinical Trial Registry was waived by the institutional review board.

Patient consent for publication

An informed consent form was signed by the relatives of the patients regarding publication of the anonymized information of the patients in the form of an article before surgeries.

Competing interests

The authors declared that they have no competing interests.

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