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A Single-Center Retrospective Study of Selected Clinical Parameters and Intraoperative Fluid Management of Patients Undergoing Pancreatoduodenectomy

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Background: Pancreatoduodenectomy is an extensive procedure with a very high risk of complications. Appropriate intraoperative fluid therapy is a subject of ongoing debate. The aim of this retrospective study was to analyze the relationship between selected preoperative parameters, intraoperative fluid therapy, and catecholamines administration during pancreatoduodenectomy.

Material/Methods: From 2011 through 2017, among pancreatoduodenectomies performed at a single university hospital, 192 patients met the inclusion criteria of the study: 105 (54.7%) males and 87 (45.3%) females with a mean age of 60.06 (±11.63) years. Correlations were assessed between sex, age, body mass index (BMI), selected comorbidities, surgery duration, American Society of Anesthesiologists (ASA) Physical Status (PS) scale, preoperative endoscopic retrograde cholangiopancreatography (ERCP) and intraoperative catecholamine administration, intraoperative fluid supply, red blood cell (RBC) concentrate and fresh frozen plasma (FFP) supply, blood loss, and diuresis.

Results: A need for catecholamines has been shown to be more frequent in smokers (P=0.01), patients with cardiovascular comorbidities (P=0.037), high ASA PS scores (P=0.003), and preoperative ERCP (P=0.011). The need for intraoperative transfusion of RBC concentrate was more frequent in smokers (P=0.005). Surgical time was significantly longer in males (P=0.014). Among females, liberal intraoperative fluid therapy (>7.9 ml/kg/h) was more frequent in patients with thyroid comorbidities (P=0.003).

Conclusions: The findings of this retrospective study demonstrate the influence of comorbidities, ASA PS class, and catecholamine use on fluid therapy during pancreatoduodenectomy.

Keywords: Catecholamines • Comorbidity • Fluid Therapy • Pancreatic Cancer, Adult • Pancreaticoduodenectomy • Retrospective Studies

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Background

Pancreatoduodenectomy is an extensive procedure with a very high risk of complications [1]. It is mainly used to treat tumors in the pancreaticoduodenal region. It has been shown that one of the primary methods to reduce perioperative and postoperative mortality is to have the procedure performed by a team of experienced surgeons in highly specialized surgical centers [2]. Intraoperative fluid supply is among the factors that can result in postoperative complications. Appropriate perioperative fluid management remains a subject of controversy [3-5]. Very low fluid volumes cause dehydration and electrolyte disturbances, while too much fluid reloading can lead to complications from the circulatory, respiratory, and gastrointestinal systems [6]. In the past, the recommended range of fluid administration in patients undergoing intra-abdominal surgery was 10 to 15 mL/kg/h with additional fluid supplementation depending on the volume of blood loss [7]. Many studies were performed comparing restrictive with liberal administration of fluid therapy, usually in favor of the former [8-13]. Few studies have compared the effects of preoperative factors on intraoperative fluid therapy and the need for intraoperative catecholamines usage. The aim of this study was to analyze the relationship between selected preoperative factors, including body mass index (BMI), comorbidities, the ASA PS (American Society of Anesthesiologists Physical Status classification system [14]), and intraoperative fluid therapy (restrictive and liberal), as well as the need for catecholamine administration during pancreatoduodenectomy. Our goal was to analyze preoperative factors that can influence intraoperative fluid therapy and catecholamine administration in order to be able to take them into account when planning and performing a major surgery such as pancreatoduodenectomy.

Material and Methods

Data from 350 consecutive patients who had undergone pancreatoduodenectomy for pancreaticoduodenal region tumors at our university medical center from 2011 through 2017 were retrospectively analyzed.

The following inclusion criteria were defined:
- age ≥18 years;
- histopathologically confirmed carcinoma of the pancreaticoduodenal region (carcinoma of the papilla of Vater, head of the pancreas, and distal common bile duct);
- resectable or borderline resectable tumors according to NCCN guidelines [15];
- pancreatoduodenectomies (Whipple and Traverso method) without vascular (portal vein, superior mesenteric vein, superior mesenteric artery, celiac artery and common hepatic artery) or multiorgan resections (except for organs that are removed as a result of the scope of surgery) that could significantly increase the length of the procedure;
- pancreatoduodenectomies performed by a surgeon with extensive experience in pancreatic surgery (defined as ≥20 pancreatoduodenectomies per year) [16];
- availability of medical records on the analyzed data;
- no active inflammation, ie, CRP below 10 International Units (IU) to eliminate the effect of the inflammatory process on the patient's fluid balance.

Regardless of the monitoring technique, analgesics, diuretics, anesthetics, and other medications were administered during anesthesia according to the current guidelines; no intraoperative complications were reported by the anesthesiologist.

The exclusion criteria were as follows:
- mixed neoplasms (neuroendocrine tumor of the pancreas with adenocarcinoma) were ruled out in order to ensure study group homogeneity; furthermore, according to several authors, the neuroendocrine component may increase the risk of complications [17];
- adenocarcinoma foci identified within mucinous cystic neoplasm or intraductal papillary mucinous neoplasm on postoperative histology;
- questionable interpretation of pancreatic texture by the operating surgeon and lack of data on Wirsung duct diameter/discrepancy between the duct's diameter on preoperative diagnostic imaging and intraoperative evaluation;
- intraoperative complications that required non-standard management (eg, pneumothorax, myocardial infarctions) to eliminate any modifications to standard fluid therapy'
- symptomatic inflammation and positive preoperative blood or bile cultures despite low CRP levels to eliminate the effect of the inflammatory process on the patient's fluid balance;
- a history of other neoplasms (treated with chemotherapy, radiotherapy, or surgery) occurring less than 12 months before pancreatoduodenectomy; in particular, recent surgical treatment can affect the course of surgery and its postoperative complications.

Following the application of the above inclusion and exclusion criteria, 192 patients were found eligible for analysis.

There was no statistically significant difference between the Wirsung duct (<3 mm vs ≥3 mm) and pancreatic gland texture subgroups (soft vs non-soft pancreas) regarding the study parameters. Hence, all 192 patients were ultimately included in the study.

Patients' Characteristics

Patients were treated in accordance with the most recent ESMO guidelines [18]. Multidisciplinary treatment included

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collaboration of a surgeon with a gastroenterologist, radiologist, and oncologist. Prior to surgical treatment, radiological and endoscopic examinations (endoscopic ultrasound [EUS] and computed tomography) were carried out. Pancreatoduodenectomies were performed by 3 experienced pancreatic surgeons.

Analysis of Intraoperative Factors

The relationships between sex, age, BMI, patients' comorbidities, ASA PS score, duration of surgery and fluid administration (colloids, crystalloids), blood loss, and diuresis, and the need for red blood cell (RBC) concentrate and catecholamine supply during and after surgery were analyzed. The ASA PS classification was used to assess the clinical status of the patients before surgery [14]. Total fluid supply divided into colloids and crystalloids was determined. Fluid administration was also determined in ml/kg/h of surgery time, which allowed a BMI-independent analysis. Both the total and the ml/kg/h fluid supply were statistically analyzed. Indications for blood transfusion, catecholamine administration, and intraoperative anesthetic care were consistent with the ERAS (Enhanced Recovery After Surgery) protocol and NICE (National Institute for Health and Care Excellence) principles [19,20]. The indication for intraoperative transfusion of RBC concentrate was hemodynamic instability of the patient. Catecholamines (norepinephrine, epinephrine, dopamine, dobutamine) were administered during surgery due to patients' hemodynamic instability associated with a drop in the mean blood pressure or stroke volume. Plasma (fresh frozen plasma [FFP]) was transfused for blood loss accompanied by coagulation disorders. The use of colloids (hydroxyethyl starch [HES]) was according to the guidelines for fluid therapy [21,22]. Values defining the adequate volume of fluids administered during pancreatoduodenectomy are not clearly defined in literature [8-13,23,24]. The median total fluid supply per kilogram of the patient's weight per hour of surgery time [ml/kg/h] has been used as a criterion to differentiate between restrictive and liberal fluid therapy [4,25].

Comorbidities

We collected data on the prevalence of diabetes and cardiovascular diseases, including hypertension, ischemic heart disease, heart failure, arrhythmias, aortic aneurysms, thrombosis, atherosclerosis, severe regurgitation, and valvular stenosis. We also considered the prevalence of respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and emphysema. Considering speculations that active smoking before surgery can cause postoperative complications [26], regular smoking during the year preceding the surgery was included in the analysis as an independent risk factor. Obesity was defined by a BMI value ≥30 [27]. Renal conditions included in analysis were chronic kidney disease, need for dialysis, and post-nephrectomy status. Central nervous system (CNS) comorbidities included post-stroke status and CNS tumors. Pancreatic diseases other than adenocarcinoma were also analyzed, including chronic pancreatitis (CP) and a history of acute pancreatitis (AP). Thyroid diseases taken into account were hypothyroidism, hyperthyroidism, and autoimmune thyroid diseases. Endoscopic retrograde cholangiopancreatography (ERCP) with prosthesis placement (at least 2 weeks before surgery) was also analyzed.

Ethics Statement

This was a retrospective study of medical records and all data had been fully anonymized before we accessed them. Written informed consent was obtained from all participants. All procedures were in accordance with the 1964 Helsinki Declaration regarding medical research involving human subjects and its later amendments or comparable ethical standards. Our retrospective analysis of patients' medical records fell into a category exempt from Institutional Review Board (IRB) approval.

Statistical analysis

A descriptive analysis was performed. A confidence interval of 95% was used. The distribution of quantitative variables was analyzed. Variables closely following a normal distribution are expressed as means and standard deviation; non-normally distributed variables are given as medians with interquartile range. Correlation analysis was performed between sex, age, BMI, surgery time, comorbidities, ASA PS score and fluid supply (colloids, crystalloids), blood loss, diuresis, need for RBC transfusion during and after surgery, and need for catecholamine administration. The level of statistical significance was set at $P<0.05$. The analysis of quantitative variables was performed using the *t* test (or *t* test with independent variance estimation) and Mann-Whitney U test. Homogeneity of variance was tested using Levene's test. Analysis of nominal variables was performed using a chi-square test or Fischer's exact test when needed. The strength of correlation was calculated using the Phi coefficient for 2×2 tables or Cramer's V for larger ones. Correlations between quantitative variables were calculated using Pearson's or Spearman's analysis, and between quantitative and qualitative variables using the Eta test (to determine the correlation coefficient) and point biserial correlation (to calculate the *P* value). All analyses that involved crystalloid and colloid administration were also performed with a ml/kg/h determination to make the obtained results and correlations independent of the patients' BMI values. All calculations and statistical analyses were performed in IBM SPSS Statistics 26 (Armonk, New York, USA).

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Results

Patients' Characteristics and Comorbidities

The study group consisted of 105 males and 87 females with a mean age of 60.06 (±11.63) years; 159 (82.8%) patients were over 50 years of age and 101 (52.6%) were over 60 years of age. The characteristics of the patients and the prevalence of comorbidities are presented in **Tables 1 and 2**. The most common comorbidities were cardiovascular diseases, occurring in 107 (55.7%) patients.

Perioperative Parameters

Perioperative parameters are shown in **Tables 1 and 2**. Most patients were in ASA PS class II (110 patients – 57.3%). The median fluid supply was 7.9 ml/kg/h and this value was considered the cut-off point between restrictive (≤7.9 ml/kg/h) and liberal (>7.9 ml/kg/h) fluid therapy [4].

Correlations Between Preoperative and Intraoperative Parameters

The analyzed correlations are presented in **Tables 3-6**. Only statistically significant results are discussed below.

A statistically significant difference in surgery duration was found between the males and females (*P*=0.014); the difference was most pronounced in males with thyroid disease (*P*=0.043) and male smokers (*P*=0.049). In females, other pancreatic diseases (*P*=0.008) and preoperative ERCP (*P*=0.058) contributed the most to increased surgery duration. There was a statistically significant difference in colloid and crystalloid supply between the male and female participants (*P*=0.002 and *P*=0.002, respectively). BMI was associated with liberal fluid therapy in females (*P*=0.008).

Catecholamine administration was more frequent in patients with preoperative cardiovascular disease (*P*=0.037), those after preoperative ERCP (*P*=0.011) and in smokers (*P*=0.01) (**Table 4**). The frequency of catecholamine administration increased along with the ASA PS class (*P*=0.003).

In the female group, a positive correlation was revealed between smoking and the supply of RBC concentrate after surgery (*P*=0.017). Thyroid comorbidities significantly increased the intraoperative fluid supply (*P*=0.001). In females, liberal fluid therapy (>7.9 ml/kg/h) was significantly more common compared to the male group (*P*=0.001). In contrast, males exhibited a correlation between obesity and the use of restrictive (≤7.9 ml/kg/h) fluid therapy (*P*=0.041). All qualitative correlations, including sex-dependent ones, are shown in **Table 4**.

CNS and respiratory diseases as well as smoking were associated with higher colloid supply in males (*P*=0.022, *P*=0.018, and *P*=0.028, respectively) (**Table 5**). CNS and pancreatic diseases other than adenocarcinoma were associated with higher crystalloid supply in females (*P*=0.026, *P*<0.001, respectively).

An analysis of parameters correlated with fluid supply revealed that higher supply (ml/kg/h) was related to female sex (*P*<0.001), obesity (*P*=0.03), thyroid disease (*P*=0.001), concomitant pancreatic disease (*P*<0.001), and ASA PS class (*P*<0.05) (fluid supply increased along with the ASA PS score). Additionally, in females, higher fluid reloading (ml/kg/h) was associated with smoking (*P*=0.044), CNS disease (*P* =0.059), ASA PS class (*P*<0.05) (fluid supply increased along with the ASA PS score), and thyroid disease (*P*=0.003). Intraoperative blood loss was higher in females with a history of smoking (*P*=0.051) and renal comorbidities (*P*=0.037). All quantitative-qualitative correlations are presented in **Tables 5 and 6**.

There was no correlation between FFP intraoperative supply and preoperative parameters. Age, diabetes, CNS diseases, pancreatic diseases did not correlate with intraoperative administration of catecholamines and perioperative RBC concentrate supply. Crystalloids supply (ml) was not correlated with preoperative variables. Diabetes, cardiovascular diseases, and preoperative ERCP did not correlate with surgery duration, fluid therapy, intraoperative blood loss, and diuresis.

Discussion

There are numerous reports on the relationships between perioperative parameters and postoperative complications as well as survival of post-pancreatoduodenectomy patients [1,9,11,25,28-30]. However, few of these considered preoperative parameters and their correlations with intraoperative factors that can affect postoperative complications. Our analysis also includes sex-dependent relationships, and this has rarely been done before.

The association between intra-pancreatoduodenectomy catecholamines and preoperative parameters was rarely investigated. In our study, we noted several correlations between comorbidities and the need for catecholamine supply. **Table 4** shows the association of chronic diseases with intraoperative catecholamine administration.

In extensive procedures like pancreatoduodenectomy, intraoperative blood supply has a significant impact on the prevalence of postoperative complications such as delayed gastric emptying, pancreatic fistulas, or the length of postoperative hospital stay and overall survival [31-40]. Although Barreto et al [41] concluded that intraoperative blood transfusion was not

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Table 1. Patients' characteristics and intraoperative parameters by sex.

	M	SD	Min.	Max.
Age (years)	60.06	11.63	22.00	82.00
Weight (kg)	71.82	14.58	43.00	115.00
Height (cm)	168.82	9.70	145.00	195.00
BMI (kg/m^2)	25.12	4.28	16.00	43.16
Surgery duration* (min.)	392.99	100.03	105.00	720.00
Crystalloid supply* (ml)	3052.91	951.90	900.00	6550.00
Crystalloid supply* (ml/kg/h)	7.16	3.68	2.09	38.86
Colloid supply* (ml)	826.63	393.47	500.00	2500.00
Colloid supply* (ml/kg/h)	1.67	1.16	0.75	7.83
Total fluid volume * (ml)	3732.81	1090.88	1400	7800.00
Total fluid volume* (ml/kg/h)	8.82	3.93	2.89	38.86
Blood loss* (ml)	781.67	510.26	100.00	3600.00
Diuresis* (ml)	545.73	436.18	100.00	4600.00
Females (n=87)				
Age (years)	59.14	13.14	22.00	82.00
Weight (kg)	64.34	12.19	43.00	115.00
Height (cm)	161.05	6.34	145.00	175.00
BMI (kg/m^2)	24.87	4.89	16.61	43.16
Surgery duration* (min.)	371.41	90.85	105.00	595.00
Crystalloid supply* (ml)	2894.83	929.65	900.00	6300.00
Crystalloid supply* (ml/kg/h)	8.12	4.71	3.11	38.86
Colloid supply* (ml)	880.77	462.65	500.00	2500.00
Colloid supply * (ml/kg/h)	1.94	1.36	0.91	7.83
Total fluid volume* (ml)	3684.48	1022.69	1800.00	7800.00
Total fluid volume* (ml/kg/h)	10.06	4.85	4.97	38.86
Blood loss* (ml)	740.96	494.06	100.00	3000.00
Diuresis* (ml)	587.29	560.49	100.00	4600.00
Males (n=105)				
Age (years)	60.83	10.21	23.00	80.00
Weight (kg)	78.14	13.44	49.00	114.00
Height (cm)	175.38	6.76	159.00	195.00
BMI (kg/m^2)	25.33	3.70	16.00	38.75
Surgery duration* (min.)	410.40	104.14	205.00	720.00
Crystalloid supply* (ml)	3187.75	954.39	1300.00	6550.00
Crystalloid supply* (ml/kg/h)	6.38	2.33	2.09	13.79

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Table 1 continued. Patients' characteristics and intraoperative parameters by sex.

	M	SD	Min.	Max.
Colloid supply* (ml)	780.22	318.06	500.00	1500.00
Colloid supply * (ml/kg/h)	1.44	0.92	0.75	5.03
Total fluid volume* (ml)	3772.86	1147.64	1400	7050.00
Total fluid volume* (ml/kg/h)	7.83	2.63	2.89	17.24
Blood loss* (ml)	816.49	523.74	100.00	3600.00
Diuresis* (ml)	510.05	288.45	100.00	1400.00

n – number of patients; M – mean; SD – standard deviation; Min. and Max. – the lowest and the highest value of the distribution; BMI – Body Mass Index. * Intraoperative parameters.

Table 2. Patients' characteristics, intraoperative parameters, comorbidities, and pre-surgery ERCP by sex.

Comorbidities	Frequency (n=192)	Frequency in females (n=87)	Frequency in males (n=105)
Diabetes	57 (29.7%)	25 (28.7%)	32 (30.5%)
Cardiovascular diseases	107 (55.7%)	46 (52.9%)	61 (58.1%)
Respiratory diseases	13 (6.8%)	6 (6.9%)	7 (6.7%)
Renal diseases	37 (19.3%)	17 (19.5%)	20 (19.0%)
CNS diseases	16 (8.3%)	7 (8.0%)	9 (8.6%)
Pancreatic diseases	12 (6.3%)	5 (5.7%)	7 (6.7%)
Thyroid diseases	20 (10.4%)	15 (17.2%)	5 (4.8%)
Smoking	43 (22.4%)	16 (18.4%)	27 (25.7%)
ERCP	49 (25.5%)	17 (19.5%)	32 (30.5%)
Age >50 years	159 (82.8%)	70 (80.5%)	89 (84.8%)
Age >60 years	101 (52.6%)	45 (51.7%)	56 (53.3%)
Obesity (≥30 BMI)	20 (10.5%)	12 (13.8%)	8 (7.8%)
Catecholamine supply*	29 (15.1%)	12 (13.8%)	17 (16.2%)
RBC concentrate supply*	53 (27.6%)	25 (28.7%)	28 (27.2%)
FFP supply*	44 (22.9%)	18 (20.7%)	26 (25.2%)
RBC concentrate postoperative supply	47 (24.7%)	26 (29.9%)	21 (20.4%)
Fluid therapy (>7.9 ml/kg/h)*	80 (50.0%)	46 (64.8%)	34 (38.2%)
ASA PS I	9 (4.7%)	6 (7.0%)	3 (2.8%)
ASA PS II	110 (57.3%)	46 (53.5%)	64 (60.4%)
ASA PS III	65 (33.9%)	31 (36%)	34 (32.1%)
ASA PS IV	8 (4.1%)	3 (3.5%)	5 (4.7%)

n – number of patients; CNS – central nervous system; ERCP – endoscopic retrograde cholangiopancreatography; RBC – red blood cell; FFP – fresh frozen plasma; BMI – Body Mass Index; ASA PS – The American Society of Anesthesiologists Physical Status.
* Intraoperative parameters.

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Table 3. Correlation analysis of preoperative versus perioperative variables by sex (numerical data in the table represent *P* value, quantitative analysis).

	Surgery duration (min.)	Crystalloid supply (ml)	Crystalloid supply (ml/kg/h)	Colloid supply (ml)	Colloid supply (ml/kg/h)	Total fluid volume (ml)	Total fluid volume (ml/kg/h)	Blood loss (ml)	Diuresis (ml)
BMI	NS	0.038	<0.001*	NS	0.011*	NS	<0.001*	NS	0.131
Age	NS	NS	NS	NS	NS	NS	NS	NS	NS
Females (n=87)									
BMI	NS	NS	<0.001*	NS	NS	NS	<0.001*	NS	NS
Age	NS	NS	NS	NS	NS	NS	NS	NS	NS
Males (n=105)									
BMI	NS	NS	<0.001*	0.038*	NS	NS	<0.001*	0.029	NS
Age	NS	NS	NS	NS	NS	NS	NS	NS	NS

BMI – Body Mass Index; NS – non-significant (*P* value >0.05). * Nnegative correlation (the higher the first variable, the lower the second).

Table 4. Correlation analysis of preoperative versus perioperative variables by sex (numerical data in the table represent *P* value, qualitative analysis).

	Intraoperative administration of catecholamines	RBC concentrate intraoperative supply	RBC concentrate postoperative supply	Fluid therapy (>7.9 ml/kg/h)
Sex: Females	NS	NS	NS	0.001
Obesity (≥30 BMI)	NS	NS	NS	0.03
Cardiovascular diseases	0.037	NS	NS	NS
Renal diseases	NS	0.046	NS	NS
Thyroid diseases	NS	NS	NS	0.001
Smoking	0.01	NS	0.005	NS
ERCP	0.011	NS	NS	NS
ASA PS	0.003	0.049	NS	NS
Females (n=87)				
Respiratory diseases	0.032	NS	NS	NS
Thyroid diseases	NS	NS	NS	0.003
Smoking	0.04	NS	0.017	NS
Males (n=105)				
Obesity (≥30 BMI)	NS	NS	NS	0.041
ASA PS	0.019	NS	NS	NS

BMI – Body Mass Index; ERCP – endoscopic retrograde cholangiopancreatography; ASA PS – The American Society of Anesthesiologists Physical Status; NS – non-significant (*P* value >0.05).

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Table 5. Correlation analysis of preoperative versus perioperative variables by sex (numerical data in the table represent *P* value, qualitative-quantitative analysis).

	Surgery duration (min.)	Crystalloids supply (ml/kg/h)	Colloids supply (ml)	Colloids supply (ml/kg/h)	Total fluid volume (ml)	Total fluid volume (ml/kg/h)	Blood loss (ml)	Diuresis (ml)
Sex: Females	NS	0.002	NS	0.002	NS	<0.001	NS	NS
Pancreatic diseases	NS	0.031	NS	NS	NS	<0.001	NS	NS
ASA PS	NS	NS	NS	0.035	NS	NS	NS	NS
Females (n=87)								
Age >50 years	NS	NS	NS	0.008	0.045	NS	NS	NS
Respiratory diseases	NS	NS	NS	NS	NS	NS	NS	NS
Renal diseases	NS	NS	NS	NS	NS	NS	0.037	NS
CNS diseases	NS	0.026	NS	NS	NS	NS	NS	NS
Pancreatic diseases	0.008	<0.001	NS	NS	NS	<0.001	NS	NS
Smoking	NS	NS	NS	NS	NS	0.044	NS	NS
ASA PS	NS	0.023	NS	NS	NS	NS	NS	0.024
Males (n=105)								
Obesity (≥30 BMI)	NS	0.23	NS	0.02	NS	0.013	NS	NS
Respiratory diseases	NS	NS	NS	0.018	NS	0.039	NS	NS
CNS diseases	NS	NS	0.028	0.022	NS	NS	NS	NS
Pancreatic diseases	NS	0.013	NS	NS	NS	0.042	NS	NS
Thyroid diseases	0.043	NS	NS	NS	NS	NS	NS	NS
Smoking	0.049	NS	NS	0.028	NS	NS	NS	NS

BMI – Body Mass Index; CNS – central nervous system; ASA PS – The American Society of Anesthesiologists Physical Status; NS – non-significant (*P* value >0.05).

Table 6. Correlation analysis of preoperative versus perioperative variables by sex (numerical data in the table represent *P* value, quantitative-qualitative analysis).

	Intraoperative catecholamine supply	RBC concentrate intraoperative supply	FFP intraoperative supply	RBC concentrate postoperative supply	Fluid therapy (>7.9 ml/kg/h)
BMI	NS	NS	NS	NS	<0.001
Age	NS	NS	NS	NS	NS
Females (n=87)					
BMI	NS	NS	NS	NS	0.008
Age	NS	NS	NS	NS	NS
Males (n=105)					
BMI	NS	NS	NS	NS	0.002
Age	NS	NS	NS	NS	NS

BMI – Body Mass Index; RBC – red blood cells; FFP – fresh frozen plasma; NS – non-significant (*P* value >0.05).

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associated with postoperative morbidity, they did find that patients with renal comorbidities required intraoperative transfusions more frequently, which is consistent with our observations. We also confirmed, consistent with the results obtained by Barreto et al, that higher ASA PS scores were associated with more frequent need for intraoperative blood supply. In males, higher BMIs were correlated with greater intraoperative blood loss (*P*=0.029). In females, blood loss was greater in patients with renal comorbidities (*P*=0.037) and smokers (*P*=0.051). Smoking is rarely reported in publications as a potentially significant risk factor for complications. Interestingly, we found that patients with respiratory diseases did not require a significantly greater blood supply after pancreatoduodenectomy (*P*=0.407). Similar to other studies, we did not find any relationship between respiratory disease and intraoperative RBC administration [41]. In contrast, among smokers (*P*=0.005) this correlation was confirmed and they required more RBC transfusions. There are conflicting data regarding the association between females and intraoperative blood supply. There are publications in which female sex was a significant factor increasing the necessity for perioperative RBC supply [31], while some others indicated lower perioperative blood loss [32]. According to several authors, longer surgery (>420 min) [31,41] was also correlated with the need for RBC transfusion. In our study, these correlations were not confirmed. Yeh et al [38] suggested older age was a risk factor for transfusion [38], but our analysis did not confirm this. Pre-surgery ERCP had no effect on blood loss and, consequently, blood supply (*P*=0.855), which is consistent with Barreto et al (*P*=0.97) [41].

The duration of surgery is a very important factor that can affect postoperative prognosis [34]. According to the literature, longer surgery is associated with increases in blood loss and fluid supply; these, in turn, might result in higher postoperative mortality [34,42,43]. It is therefore crucial to identify preoperative clinical factors that influence surgery duration (**Tables 3 and 5**). We found a statistically significant difference (*P*=0.014) in surgery time between the male (mean 410±104 min) and the female groups (mean 371±90 min). In addition, a difference was observed between males and females regarding the effect of comorbidities on the duration of surgery. Relationships between BMI and surgery time were discussed in a study by Tang et al [44]. In males, smoking was associated with longer operative time (*P*=0.049); this correlation had not been previously reported. Thyroid comorbidities increased surgery time in males (*P*=0.043). In females, longer surgery time was correlated with pancreatic disease other than adenocarcinoma (*P*=0.008) and pre-surgery ERCP (*P*=0.058). The above-mentioned relationships have also not been widely described in the available publications.

The determination of appropriate fluid therapy for extensive abdominal procedures, including pancreatoduodenectomy, remains controversial [4]. According to Myles et al [11], restrictive (≤3 liters of total fluid volume) and liberal fluid therapy (≥5 liters of total fluid volume) have both advantages and drawbacks. According to Gottin et al [45], significantly fewer postoperative complications (eg, postoperative fistula, abdominal collection, and hemorrhage) were found in the restrictive fluid therapy group (≤4 ml/kg/h) than in patients who had received liberal fluid therapy (≥12 ml/kg/h). Gilgien et al [46] also concluded that patients who received ≥4400 ml intravenous fluids during the first 24 h after surgery had more complications, especially pulmonary complications. Liberal fluid therapy may also lead to an increase in postoperative pancreatic fistula (POFF) formation [47]. Some authors argue that both ultra-restrictive and ultra-liberal fluid therapy are not optimal [48]. Patients managed with ultra-restrictive fluid regimens are prone to hypotension, acidosis, and reduced interstitial volume. In contrast, patients receiving high volumes of fluids can develop interstitial tissue edema and hemoglobin dilution. It is worth pointing out that a more restrictive fluid regimen during pancreatoduodenectomy does not lead to an increase in postoperative acute kidney injury [49]. However, it has also been suggested that there is no association between the amount of perioperative intravenous fluid administered and postoperative complications (including the length of hospital stay, estimated blood loss, pancreas specific complications or 30-day mortality) in patients undergoing pancreatoduodenectomy [50,51].

The factors determining the type of fluid therapy during the procedure are still a matter of debate [52]. In our study, we analyzed the relationship between preoperative parameters and the fluid therapy administered, with an additional division into colloids and crystalloids. Similar to Wang et al [25], we separated restrictive and liberal fluid therapy, taking as a cut-off point the median volume of fluids administered per kilogram of patient weight per hour of surgery (ml/kg/h), with a result of 7.9 ml/kg/h [25].

Iwasaki et al designed an interesting pilot study that compared the intraoperative fluid balance and perioperative complications in patients undergoing hepato-biliary-pancreatic surgery with or without stroke volume variation (SVV)-guided fluid management [53]. They concluded that the use of the SVV-guided fluid management protocol did not reduce intraoperative fluid balance, but increased the intraoperative fluid administration and might worsen postoperative oxygenation (*P*=0.019).

As seen in recently published work of Lapisatepun et al, postoperative fluid balance was a modifiable risk factor reducing the incidence of clinically relevant postoperative pancreatic fistula (CR-POFF) [54]. Similar findings were reported by Winer et al [55], in which CR-POFF was correlated with high 72-h net fluid balance. Higher positive postoperative fluid balance

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at postoperative day 3 should be avoided, especially in higher CR-POPF risk patients. However, a prospective randomized controlled trial shows that in high-volume centers there is not any difference in major postoperative complications such as 60-day mortality or clinically relevant complications (≥3) in Clavien-Dindo scale between restrictive (≤6 ml/kg/h) and liberal (≥12 ml/kg/h) fluid regimens [56]. Sandini et al evaluated 9 different fluid regimens [57], concluding that total volume administration of >5000 ml and >6000 ml of fluids was associated with increased complications and >6000 ml was associated with increased risk of sepsis. Additionally, a rate of <5 ml/kg/h was associated with increased risk of postoperative pancreatic fistula and sepsis, <6.8 ml/kg/h fluid regimen was associated with increased major morbidity and sepsis, and <8.2 ml/kg/h was associated with increased POFF. There were no effects observed on pulmonary complications, surgical site infections, length of stay, or mortality. Differing fluid therapy regimens do not have any significant effect on occurrence of delayed gastric emptying and its emptying time [58].

Patients' BMI is another parameter considered in studies on intraoperative fluid therapy. Obesity can lead to a number of post-pancreatoduodenectomy complications, including wound infection, septic shock, and death [12,43,59,60], but other authors found no such relationship [4,61]. However, the relationship between BMI and fluid administration has only rarely been considered. Our study revealed that obesity in males was associated with restrictive (≤7.9 ml/kg/h) fluid therapy (*P*=0.041).

The relationship between sex and intraoperative fluid supply has not been clarified so far. According to some authors, females require higher fluid volumes more often than do male patients [9,62]. There are also reports that males, require higher fluid supply up to twice as often [63]. Our study demonstrated that intra-pancreatoduodenectomy liberal fluid therapy (>7.9 ml/kg/h) was significantly more frequent in females (*P*=0.001). Furthermore, among females, the volume of administered colloids was significantly higher (ml/kg/h) in female patients older than 50 years (*P*=0.008).

The risk for intraoperative and postoperative complications increases with higher ASA PS scores [14]. If surgery becomes complicated due to increased blood loss, patients are more likely to require increased fluid supply [11]. According to the literature, patients whose ASA PS score is ≥3 are about 1.5 times more likely to require increased fluid therapy [62,63]. In our study, this relationship was demonstrated with respect to colloids (Eta=0.28, *P*<0.05). On the other hand, a significantly higher supply of crystalloids was observed only in females (Eta=0.221, *P*<0.05).

In our analysis, higher ASA PS scores were associated with greater intraoperative blood loss; in females, urine excretion increased as well (Eta=0.295, *P*<0.05). While searching for reports in the literature on the relationship between volume of blood lost or intensity of intraoperative fluid therapy and diuresis, we came across the work of Ishihara et al [64], who observed an association between increased volume of fluids administered and higher diuresis in a group of patients where goal-directed therapy principles were followed [30,64]. Czajka et al [65] also reported a positive correlation between blood loss and ASA PS class.

Patients undergoing pancreatoduodenectomy are frequently older individuals (the mean age of our patients was 60.06±11.63 years) with concomitant diseases. Consequently, the rates of postoperative complications and mortality tend to be higher [66-68]. We determined the relationships between comorbidities and intraoperative fluid supply. Co-occurrence of thyroid disease was significantly correlated with higher fluid reloading during surgery (*P*=0.001). CNS diseases were correlated with higher colloid supply in males (*P*=0.022) and higher crystalloid administration in females (*P*=0.026). Pancreatic diseases were significantly associated with higher fluid supply (ml/kg/h) (*P*=0.042 in males, *P*<0.001 in females). Smoking was correlated with increased colloid supply (ml/kg/h) in males (*P*=0.028) and total fluid volume (ml/kg/h) in females (*P*=0.044). As shown above, several preoperative clinical parameters can influence the volume of intraoperatively administered fluids and, consequently, the incidence of postoperative complications.

To sum up:

A need for catecholamine use was more frequent in smokers and in patients with cardiovascular diseases, higher ASA PS scores, and pre-surgery ERCP. Intraoperative RBC transfusions were more frequently used in patients with renal diseases and higher ASA PS scores. Post-surgery RBC administration was more frequent in smokers and patients with respiratory diseases. In males, higher BMIs were associated with greater intraoperative blood loss, whereas in females, blood loss was greater in patients with renal comorbidities and smoking. The duration of surgery was significantly longer in males. Liberal intraoperative fluid therapy (>7.9 ml/kg/h) was significantly more frequent in women with higher ASA PS and those with thyroid disease.

There are some limitations to our research. It was a single-center retrospective study and it was restricted to 192 patients. There may be some bias that could have been introduced by the long duration of the study. Our results might have been influenced by comorbidities other than those included in the analysis. Despite the defined standards of intraoperative anesthesia, patient management could have included administration of some other medications that could also affect the patient's condition. Two types of anastomoses were used

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– duct-to-mucosa and end-to-end invagination. However, as surgery duration and fluid therapy were comparable, we believe anastomotic techniques did not have any significant effect on the patients' outcomes.

Conclusions

There are some preoperative factors that can influence intraoperative fluid therapy and catecholamine administration. Those that might have a significant impact on the intraoperative care are the ASA PS score, BMI, smoking, and certain comorbidities. These should therefore be taken into account when planning and performing a major surgery such as pancreatoduodenectomy.

Data Availability Statement

The data that support the findings of this study are openly available in Kaggle at https://www.kaggle.com/patrykzemla/pd-raw-db. Raw data were generated at the Department of Gastrointestinal Surgery, Medical University of Silesia, Katowice, Poland.

Department and Institution Where Work Was Done

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