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Complications after pancreaticoduodenectomy are associated with higher amounts of intra- and postoperative fluid therapy: A single center retrospective cohort study

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HIGHLIGHTS

- High amounts of perioperative fluid may impair surgical outcome of pancreatic resection.
- >6000 ml intraoperative fluid was associated with more infectious complications.
- >14 000 ml total fluid by postoperative day 5 was linked with many complications.
- Complications included infections, fistulas, delayed gastric emptying and bleeding.
- Prospective randomized controlled trials should investigate postoperative fluid therapy.

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ABSTRACT

Background: Perioperative mortality after pancreaticoduodenectomy has decreased significantly in high-volume centers, but morbidity remains high. Restrictive perioperative fluid management may contribute to reduced complication rates after various surgical procedures. The aim of this study was to determine whether there is a correlation between the amount of fluid administered and postoperative complications. We hypothesized that higher amounts of intra- and total fluid is associated with greater postoperative morbidity.
Materials and methods: We retrospectively examined data of 553 patients who underwent pancreaticoduodenectomy at University of Freiburg Medical Center between 2001 and 2013. Data on intra - and postoperative fluid administration (until postoperative day 5) were obtained from anesthesiological and surgical records. Data on complications were retrieved from our institutional pancreatic database.
Results: The median values for intra- and total fluid administered were 6000 ml (range 400–15,000 ml) and 13,600 ml (range 5000–57,700 ml), respectively. The overall in-hospital mortality was 1.9% (no correlation with fluid administration). Patients who received more than 6000 ml intraoperative fluid had more wound infections ($P = 0.049$), intra-abdominal abscesses ($P = 0.020$) and postoperative interventions ($P = 0.007$). In patients who received more than 14000 ml fluid until postoperative day 5 all evaluated types of postoperative complications (infectious, fistula, delayed gastric emptying, bleeding) and re-interventions occurred significantly more frequently than in patients who received less than 14,000 ml ($P < 0.05$–0.001).
Conclusions: Higher amounts of fluids may contribute to postoperative complications. More studies are needed to adequately assess the use of intra/postop fluid therapy.

1. Introduction

Pancreaticoduodenectomy (PD) has become a routine operation in many parts of the world. It is performed mostly for

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periampullary malignancies, but also for chronic pancreatitis and cystic lesions of the pancreas. Although perioperative mortality has decreased to 1–5% over the last decades in high-volume centers [1,2], perioperative morbidity rates still range from 30 to 60% [2–5]. Common postoperative complications are wound infections, delayed gastric emptying (DGE) and pancreatic fistula (POPF). POPF occur in 9–40% in large studies [5–9], impact patient comfort, and lead to prolonged hospital stay as well as higher re-admission and re-intervention rates [5–7], POPF may even cause fatal complications such as sepsis induced by intra-abdominal abscesses or hemorrhage evoked by ruptured intra-abdominal aneurysms [10], and increases the risk of cancer recurrence [11]. Therefore, causal factors of postoperative complications after PD must be better identified and targeted.

Controversy exists concerning optimal perioperative fluid management for patients undergoing major abdominal surgery [12,13]. Liberal intraoperative (IOF) and postoperative fluid (POF) administration has been found to impact healing of intestinal anastomoses following colorectal surgery [12,14,15] and in experimental models [16,17].

Few studies have investigated the influence of perioperative fluid regimens on the outcome after pancreatic resections. The results are contradictory; some suggest that excessive use of intraoperative fluid leads to more postoperative morbidity and mortality [18–23], while others do not find these associations [13,24,25].

The clinical relevance of *post*operative fluid therapy for postoperative complications remains unclear and has been investigated in only very rare studies [21,23]. The aim of this study was to determine whether there is a correlation between the amount of fluid administered and postoperative complications in a cohort of over 550 patients who underwent PD. The hypothesis was that higher amounts of fluid were associated with more postoperative complications.

1.1. Patients and methods

A retrospective exploratory data analysis of a pancreatic database was done to identify patients who underwent PD for various pathologies. The cohort study is consistent with the STROBE criteria [26]. Between 2001 and 2013, 553 pancreaticoduodenectomies were performed at our institution; 138 of the operations included additional vascular resections (25%). Pancreatogastrostomy (57%) or pancreaticojejunostomy (43%) was used as reconstruction technique. Patients with total pancreatectomy (n = 42) were excluded from the analysis to reach better comparability. Data on fluid administration were extracted from anesthesiologic protocols and surgical patient charts. The postoperative follow-up was performed by the institutional specialized pancreatic outpatient clinic; follow-up was a minimum of 2.5 years. Loss to follow-up was not addressed in this study since the observed complications usually occur during the hospital stay or shortly after discharge. The local Ethics Committee approved the study.

IOF was defined as the amount of all types of intravenously-administered fluid in the operation theatre until the end of the surgical procedure. TF_POD5 was defined as the amount of all intravenously-given fluid until the end of postoperative day 5 (including IOF). To evaluate the impact of fluid on postoperative complications, four groups of fluid administration were defined as quantitative variables: ≤6000 ml of total IOF and >6000 ml of total IOF. The groups were chosen due to the median amount of IOF: 6000 ml. The other two groups were ≤14 000 ml and >14 000 ml TF POD5, since the median amount of total fluid administered by postoperative day 5 was 13,600 ml.

Neither anesthetic nor postoperative surgical intensive care unit (SICU) treatment algorithms were strictly standardized at our institution. However, 71%of the patients received an epidural catheter for intra- and postoperative pain management, and blood product transfusions were generally initiated at hemoglobin levels below 8 g/dl in patients without coronary artery disease (CAD) and less than 10 g/dl in patients with CAD. Additionally, patients usually received 1 ml/kg/h of Normofundin® G-5 (Braun, Melsungen, Germany) on the day of operation upon admission to the SICU. In the operating room and on the SICU, blood pressure (systolic pressure goal >90 mmHg or no decrease from baseline > 15–20%) and urine output (targeting 0.3–0.5 ml/kg/h) were monitored. Noradrenalin was the standard perioperative catecholamine used in almost all cases.

Delayed gastric emptying (DGE) [27], POPF and post-pancreatectomy hemorrhage (PPH) were defined and classified by the International Study Group Pancreatic Surgery (ISGPS) into A, B and C [28]. Type A POPF were partially included in the "no POPF" group in this analysis due to its limited clinical impact. To avoid potential bias, trained special nurses, who were not informed about any potential outcome interests, collected all medical record information. Comorbidities such as body mass index (BMI) preoperative diabetes, preoperative kidney function as well as a history of tobacco or alcohol abuse were recorded. Due to the long time period of 12 years, two time periods were chosen: time period one (2001–2008. N = 276) and time period two (2009–2013 N = 277) and compared for several variables.

1.2. Statistical analysis

Data analysis was performed with IBM SPSS Statistics for Windows (Version 23; Armonk, NY USA: IBM Corp.). The level of significance was defined as <0.05. For descriptive analysis we used non-parametric tests such as the Kruskal-Wallis and the Mann-Whitney-U test. Scale variables were expressed as median and range, categorical parameters as absolute count and percentage. Study parameters were sex, age, American Society of Anesthesiologists (ASA) classification, BMI, risk factors, laboratory findings, disease type, and the amount of fluid administered, as well as complications. Evaluated complications were POPF, DGE, intra-abdominal abscess, wound-infection, postpancreatectomy hemorrhage (PPH), postoperative interventions, operative revision, overall complications, operation-associated complications, in-hospital mortality and 30-day mortality. POPF, DGE and PPH were defined and graded according to the ISGPS criteria [26–29]. Operation-associated complications included POPF, PPH, DGE, wound infection, intra-abdominal abscess, post-operative intervention and re-operation. All variables included in the analysis are depicted in Tables 3 and 4. Several study parameters such as POPF and intra-abdominal abscesses are naturally connected and thus confound the analysis. If relevant, these are discussed in further detail in the discussion section. In rare cases, missing variables were secondarily extracted from the medical records.

2. Results

2.1. Patient demographics

Between 2001 and 2013, 553 patients underwent pancreaticoduodenectomy at our institution. The sex of the patients was almost equally distributed, and the median age was 66 years (Table 1). Comorbidity was classified as ASA II in more than half of the patients, but one-third was ASA III. Median body mass index (BMI) was 24.3 kg/m^2. More than 90% of patients had a BMI <30 kg/m^2. Preoperative diabetes was recorded in 25% of patients. Preoperative kidney function was sufficient with creatinine-levels of

Table 1
Characteristics of 553 patients undergoing pancreatic head resection.

Parameter		n (%)	Median [range]
Total population		553 (100)	
Sex	female	275 (49.7)	
	male	278 (50.3)	
Age (years)			66 [19–89]
ASA Classification			2.0 [1–4]
ASA	I	35 (7.5)	
	II	269 (58)	
	III	156 (33.6)	
	IV	4 (0.9)	
Preoperative body weight (BMI)			24.3 [15.1–41.2]
BMI (kg/m^2)	<30	501 (90.6)	
	≥30	52 (9.4)	
Comorbidities and risk factors			
Diabetes mellitus		140 (25.3)	
Creatinine (mg/dl)	≤0,9	430 (77.8)	
	>0,9	123 (22.2)	
Nicotine abuse		121 (25.5)	
Alcohol abuse		74 (15.4)	
Preoperative laboratory findings			
Creatinine (mg/dl)			0.79 [0.3–4.3]
Hemoglobin (g/dl)			13.0 [8.5–17.5]
Total bilirubin (mg/dl)			0.8 [0.1–37.4]
Disease			
Pancreatic cancer		246 (44.5)	
Chronic pancreatitis		84 (15.2)	
Other malignancies		77 (13.9)	
Ampullary carcinoma		64 (11.6)	
Benign lesions/other		63 (11.4)	
Neuroendocrine pancreatic cancer		19 (3.4)	
Operation technique			
Whipple		60 (10.8)	
PPPD		493 (89.2)	
Reconstruction technique			
Pancreatogastrostomy		316 (57.1)	
Pancreaticojejunostomy		237 (42.9)	

SI conversion factors: To convert hemoglobin to g/L, multiply values by 10; to convert creatinine to μmol/L, multiply values by 88.4; to convert total bilirubin to μmol/L, multiply values by 17.104.

<0.9 mg/dl in about 78% of patients (n = 430). About 25% (n = 121) of patients were smokers, and 15% (n = 74) had a history of alcohol abuse.

The most frequent reason for pancreatic head resection was pancreatic cancer (45%; n = 246), followed by chronic pancreatitis (15%; n = 84). All demographic parameters are listed in Table 1.

2.2. Intraoperative (IOF) and postoperative fluid management

The median amount of intraoperatively administered fluid (IOF) was 6000 ml (range 400–15000 ml). Packed red blood cells (PBC) were administered in 20.6% of the cases (n = 114) with a median amount of 600 ml (range 300–4500 ml), while fresh frozen plasma (FFP) was given only in 10.8% of cases (n = 60). Almost all patients had intraoperative catecholamine therapy. The median operating time was 426 min (Table 2). The median amount of additional fluid administered postoperatively on the day of surgery was 1600 ml (total amount of fluid administered on the day of operation: 7600 ml; range 2300–18400 ml; Table 2). In total, patients received a median of 13,600 ml of intravenous fluid by end of POD5 (TF_POD5, including IOF).

One hundred eighty-one patients (32.7%) received blood transfusion during the first 5 days (surgery included). FFPs were administered postoperatively in 17.9% (n = 99) of patients. More than 65% of patients received at least one dosage of diuretics postoperatively to reach the targeted urine output (0.3–0.5 ml/kg/h), and about 60% received catecholamines. The cumulative drain output was 2900 ml (400–17200 ml) by POD5.

2.3. Postoperative mortality and morbidity

The 30-day mortality was 1.1% (n = 6), and in-hospital mortality was 1.9% (n = 11). Causes of mortality were prolonged sepsis, heart attack, PPH and pulmonary embolism and were not associated with IOF or POD5 (Tables 3 and 4). Overall morbidity was 59.5% (n = 329). Surgery-related complications occurred in 44.7% (n = 247), type B or C pancreatic fistulas in 8.9% (n = 49) and 6.3% (n = 35), respectively. DGE grade B/C was documented in 14.1% (n = 78), wound infections in 16.6% (n = 92). Postoperative bleeding (PPH, all grades) occurred in 9.8% (n = 54). “Early” PPH (within the first 5 postoperative days) was documented in 19 cases and occurred in median on day 1; “late” PPH (after the 5th postoperative day, median on day 11) occurred in 35 cases.

Postoperative interventions for complications were necessary in 28.3% (n = 157), whereas 12.1% (n = 67) underwent relaparotomy.

2.4. Intraoperative fluid, total fluid and perioperative outcome

In the subgroup of patients with >6000 ml IOF, overall complications ($P = 0.006$), wound infections ($P = 0.049$), and intra-abdominal abscesses ($P = 0.020$) occurred significantly more often than in patients with ≤6000 ml IOF (Table 3). Additionally this group had more therapeutic interventions (34% vs 24%; $P = 0.058$). It is of note that IOF was not associated with early PPH occurring within the first 5 postoperative days. However, patients who received >6000 ml IOF had significantly more late PPH (after POD 5; $P < 0.03$; Table 3). Thirty-day mortality in the subgroup with higher amounts of IOF showed a trend towards significance, however, this p-value, unfortunately, does not prove significance (2% vs 0.3%; $P = 0.058$). Interestingly, the total amount of fluid given until the end of postoperative day 5 (TF_POD5) correlated more strongly with perioperative outcome. The group of patients who received more than 14,000 ml of fluid until POD5 had significantly more of all investigated types of postoperative complications, except in-hospital- and 30-day mortality (Table 4). TF_POD5 was independently associated with both early and late PPH occurring within or after the first 5 postoperative days (both $P < 0.01$; Table 4).

It is of note that longer operating time was significantly correlated with more IOF: Patients with an operating time of ≤420 min received (in median) 5000 ml IOF, whereas longer operating time (>420 min) was associated with a median IOF of 7000 ml ($p < 0.001$). This volume-difference of about 2000 ml between the groups with shorter or longer operations persisted for the total volume administered until postoperative day 5 (TF_POD5 12,400 ml vs 14,500 ml; $p < 0.001$). Moreover, patients with an epidural catheter (n = 391, 71%) received significantly less IOF and total fluid ($p = 0.000$). Additionally, patients with several comorbidities were evaluated separately. Patients with coronary artery disease did not receive higher or lower amounts of intraoperative fluid ($p = 0.205$). Preoperative elevated creatinine levels did not correlate with the amounts of intraoperative fluid- there was however a trend towards significance ($p = 0.07$).

A median operating time of 426 min is long. This is mostly due to the fact that we are a large academic hospital and we not only operate more complex cases (25% vascular resection rate), but also conduct intraoperative teaching: operating steps such as the hepaticojejunostomy, gastrojejunosotmy or removal of the gall bladder can be done by fellows or residents, this takes time. When we additionally compared time period one and two, we found that operating time decreased significantly (450–402 min; $P = 0.00$) more patients received epidural catheters for pain management (53

Table 2
Perioperative fluid management in 553 patients undergoing pancreaticoduodenectomy.

Parameter		n (%)	Median [range]
Intraoperative			
Total fluid administered (ml)		553 (100)	6000 [400–15,300]
PBC (ml)		114 (20.6)	600 [300–4500]
FFP (ml)		60 (10.8)	800 [400–2800]
Catecholamines		540 (97.6)	
Operation time (min)			426 [152–963]
Total until POD 5			
Total fluid administered (ml)	Σ OP-day	553 (100)	7600 [2300–18400]
	Σ until POD 1	553 (100)	9700 [4500–21,500]
	Σ until POD 2	553 (100)	11100 [4600–30,400]
	Σ until POD 3	553 (100)	12000 [4700–39,900]
	Σ until POD 4	553 (100)	12800 [4800–48,500]
	Σ until POD5	553 (100)	13600 [5000–57,700]
PBC (ml)	Σ OP - POD 5	181 (32.7)	600 [300–4500]
	Σ POD 1-5	103 (18.6)	600 [300–2400]
FFP (ml)	Σ OP - POD 5	99 (17.9)	800 [200–7000]
	Σ POD 1-5	55 (9.9)	400 [200–5800]
Postoperative until POD 5			
Catecholamines		334 (60.4)	
Diuretics		362 (65.5)	
Drainage- output until POD 5 (ml)			2900 [400–17,200]

PBC, packed red blood cells; FFP, fresh frozen plasma; POD, postoperative day; Total fluid administered contains colloids, crystalloids, PBC, FFP; PPPD, Pylorus preserving pancreaticoduodenectomy; Σ = sum.

Table 3
Postoperative complications in correlation with intraoperative fluid therapy.

Parameter		Intraoperative fluid		
		Σ = 6000 ml N = 304	Σ > 6000 ml N = 249	*P*
In-hospital		6 (2.0%)	5 (2.0%)	0.977
30-day mortality		1 (0.3%)	5 (2.0%)	0.058
Postoperative complications				
Any complication		165 (54%)	164 (66%)	0.006
Operation-associated Complication		128 (42%)	119 (48%)	0.181
POPF B/C		41 (13%)	43 (17%)	0.218
POPF groups (type)	A	61 (20%)	44 (18%)	0.169
	B	28 (9%)	21 (8%)	
	C	13 (4%)	22 (9%)	
Postpancreatectomy hemmorhage (PPH)		24 (8%)	30 (12%)	0.07
PPH POD 0 - 5		11 (4%)	8 (4%)	0.88
PPH after POD 5		13 (4%)	22 (9%)	< **0.03**
Delayed gastric emptying (DGE)	A	137 (50%)	102 (48%)	0.395
	B	36 (13%)	19 (9%)	
	C	11 (4%)	12 (6%)	
Infectious complications				
Wound infection		42 (14%)	50 (20%)	**0.049**
Intraabdominal abscess		25 (8%)	36 (15%)	**0.020**
Operative revision & intervention				
Post-OP intervention		72 (24%)	85 (34%)	**0.007**
Operative revision		36 (12%)	31 (12%)	0.828

POPF, postoperative pancreatic fistula, includes types B and C according to Bassi et al.; PPH, postpancreatectomy hemorrhage, includes types A, B and C according to Wente et al.; DGE, delayed gastric emptying type A, B and C according to Wente et al. Statistically significant complications are displayed in bold type.

vs 89%; $P = 0.00$), fewer patients received intraoperative blood transfusions, and most importantly patients received less median intraoperative and less total fluid (IOF = 6500 ml vs. 5700 ml, POD_5 = 16,000 ml vs 12000 ml; $P = 0.00$).

3. Discussion

We carried out a single-center retrospective cohort study of 553 patients undergoing PD to assess the impact of intraoperative and postoperative fluid therapy on postoperative complications. This is a large patient cohort; other studies from the field include 98–577 patients [18–23,25].

Table 4
Postoperative complications in correlation with total fluid volume until post-operative day 5.

Parameter		Total Fluid POD#5		
		Σ = 14 000 ml N = 302	Σ > 14 000 N = 251	*P*
Mortality				
In-hospital		3 (1.0%)	8 (3.2%)	0.66
30-day mortality		2 (0.7%)	4 (1.6%)	0.293
Postoperative complications				
Any complication		150 (50%)	179 (71%)	<0.001
Operation-associated Complication		113 (37%)	134 (53%)	<0.001
POPF B/C		34 (11%)	50 (20%)	0.005
POPF groups (type)	A	51 (17%)	54 (21%)	< **0.001**
	B	25 (8%)	24 (10%)	
	C	9 (3%)	26 (10%)	
Postpancreatectomy hemmorhage (PPH)		17 (6%)	37 (15%)	< **0.001**
PPH POD#0 -#5		5 (2%)	14 (6%)	< **0.01**
PPH after POD#5		12 (4%)	23 (10%)	< **0.01**
Delayed gastric emptying (DGE)	A	156 (55%)	83 (40%)	< **0.001**
	B	34 (12%)	21 (10%)	
	C	7 (3%)	16 (8%)	
Infectious complications				
Wound infection		37 (12%)	55 (22%)	**0.002**
Intraabdominal abscess		19 (6%)	42 (17%)	< **0.001**
Operative revision & intervention				
Post-OP Intervention		58 (19%)	99 (39%)	< **0.001**
Operative revision		24 (8%)	43 (17%)	< **0.001**

Σ total POF (postoperative day) includes crystalloids, colloids, erythrocyte concentrates, fresh frozen plasma until POD 5.
POPF, postoperative pancreatic fistula, includes types B and C according to Bassi et al.; PPH, postpancreatectomy hemorrhage, includes types A, B and C according to Wente et al.; DGE, delayed gastric emptying type A, B and C according to Wente et al. Statistically significant complications are displayed in bold type.

We found more postoperative complications in the group of patients who received more intra-and postoperative fluids. Infectious- and overall complications were recorded more often in patients with higher amounts of intraoperative fluid administered. More importantly, all investigated complications including operation-associated complications, infectious complications, re-intervention and re-operation were recorded significantly more frequently in the group of patients who received >14,000 ml fluid until POD5.

Recent literature from the fields of anesthesia, gastrointestinal and colorectal surgery include level 1 evidence for the benefit of using goal-directed and “restrictive” IOF management strategies [14,15]. However, most of these trials were conducted with patients undergoing colorectal surgery [14,15] and abdominal aortic repair [30,31] thus, it remains unclear whether their findings apply to PD patients. The studies on fluid management in patients undergoing PD are limited, and show contradictory results with respect to intraoperative fluid therapy and postoperative outcome [18–25]. Additionally, studies on *post*operative fluid management after PD are lacking. Most studies focus on IOF administration [13,18–20,24,25] and only few studies describe [12,21–23,30] and partly analyze [21] the postoperative phase: only one group found that higher fluid balance at 48 and 72 h postoperatively was an independent predictor of morbidity and length of stay on multivariate analysis [21].

Our study has several limitations: Specific reasons for high amounts of intraoperative fluid therapy, such as major intraoperative bleeding or preoperative dehydration, have not been assessed and can thus not be clearly discussed. Parameters like intraabdominal abscess often co-exist with DGE or POPF and are thus not independent factors. Additionally, the retrospective design allows only limited conclusions. Especially the question “what came first, the chicken or the egg?” with respect to complications and postoperative fluid therapy cannot sufficiently be answered. Potentially, patients who develop PPH, POPF, DGE, infectious complications, or have to undergo an intervention, need and receive more fluid due to the complication. This would mean that the higher amount of fluid is not causative but a result of the complication.

There are, however, arguments against this scenario. Most intra-abdominal abscesses and other investigated complications in this study occurred *after* postoperative day 5.

To further clarify a possible chronological correlation between fluid administration and subsequent complications, we re-analyzed PPH, after classification into early (until POD5) and late post-operative bleeding. Higher amounts of intraoperative fluid were not associated with early PPH (which often occurs for technical reasons, ‘surgical bleeding’) but was clearly associated with late bleeding. In addition, higher amounts of total fluid administered until POD5 correlated not only with early PPH (explained by infusions/transfusions given because of bleeding) but especially with late PPH occurring *after* the 5th postoperative day.

One may also argue that absolute amounts of fluids but not infusion rates adapted to bodyweight (ml/kg/h) are displayed here. That is correct and a limitation of this study, but we decided to use this parameter since it seems to allow better comparability, especially with respect to the postoperative phase in which fluids are usually administered only if certain physiological parameters (urine output, blood pressure) are not maintained. The amounts of fluids administered in our study are comparable to the available studies on fluid management in PD [18–25]. Despite its limitations, this large cohort of 553 patients is very homogeneous with respect to operation technique and SICU management.

A prospective randomized trial was designed to determine whether acute normovolemic hemodilution (ANH) decreases the need for allogeneic erythrocyte concentrate transfusion in patients undergoing PD. In that study, patients in the ANH group received an average of over 2 L more fluid than control patients. The authors reported that the extra volume in the ANH group led to higher frequency and greater severity of complications related to the pancreatic anastomosis (leak, fistula, abscess) [18]. Retrospective single-center studies show contradictory results. While two studies did not corroborate these findings [24,25], other studies found a significant association between fluid overload and the development of POPF [18,19], DGE [20], sepsis [20], mortality [20,21], and overall complications [21–23].

One group recently published the only single-center, randomized, and controlled trial on IOF management in PD [22]. The authors compared a “restrictive” regimen using (3%) hypertonic saline (HYS) with the standard lactated Ringer's regimen in patients undergoing PD [22]. After the day of operation, all patients received identical fluid management, thus differences in outcome appear more closely linked to fluid management on the day of the operation. The authors found a significant reduction of complications in the “restrictive” HYS-arm, but there was no statistically significant difference between the two groups regarding the development and severity of POPF or DGE. These are important findings. The study, however, compared two different fluid types and it would thus be interesting to repeat this study with a restrictive and a liberal fluid regime of the same standard fluid (e.g. lactated Ringer's solution) - and expand it to the first 3 to 5 postoperative days.

In summary, the reasons for the impact of intra- and total fluid therapy on postoperative outcome remain speculative and seem to be multifactorial: We could identify several factors that correlated with postoperative morbidity and the amount of intra-and total fluid administered: time period one against time period two (less fluid was administered in period two), intraoperative blood transfusions (less in period two), length of surgery (shorter in period two), epidural catheter (more frequent in period two), the reduction of frequency of intraoperative blood transfusions (period two).

3.1. Three learning points can be drawn from this study

First, postoperative complications still often occur after pancreatic head resections even in large referral centers. Especially fistulas and infectious complications are frequent and have to be anticipated in order to react properly. Second, intraoperative fluid management seems to affect postoperative complications and potentially a more restrictive fluid regimen is beneficial, this however, needs to be assessed in prospective randomized trials. Shorter operating times and epidural catheters additionally seem valuable. Third, the fluid regimen in the postoperative phase until POD 5 seems to be relevant for the development of postoperative complications; an advisable regime should be developed.

Currently, another prospective randomized trial of restrictive versus liberal perioperative fluid management in patients undergoing PD is being conducted at Memorial Sloan-Kettering Cancer Center (NCT01058746) and will certainly provide important information on optimal fluid management.

4. Conclusion

Higher amounts of fluids may contribute to postoperative complications. More studies are needed to correct for confounding variables and adequately assess the use of intra/postop fluid therapy.

Ethical approval

Ethical Approval has been obtained from the Ethics Committee of the University of Freiburg, (EK Freiburg ID: 430/14).

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Author contributions

Kulemann and Makowiec had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Kulemann, Marjanovic, Hoeppner, Hopt

Acquisition of data: Fritz, Sick, Makowiec, Analysis and interpretation of data: All authors.

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Conflicts of interest

None.

Registration of research studies

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Consent

Studies on patients or volunteers require ethics committee approval and fully informed written consent which should be documented in the paper.

Authors must obtain written and signed consent to publish a case report from the patient (or, where applicable, the patient's guardian or next of kin) prior to submission. We ask Authors to confirm as part of the submission process that such consent has been obtained, and the manuscript must include a statement to this effect in a consent section at the end of the manuscript, as follows: "Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

Patients have a right to privacy. Patients' and volunteers' names, initials, or hospital numbers should not be used. Images of patients or volunteers should not be used unless the information is essential for scientific purposes and explicit permission has been given as part of the consent. If such consent is made subject to any conditions, the Editor in Chief must be made aware of all such conditions.

Even where consent has been given, identifying details should be omitted if they are not essential. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note.

The ethics committee of the University of Freiburg approved the study, specific informed consent is however not necessary due to the fact that no identifiable patient characteristics are obtained or published. Most Patients however gave written informed consent for the inquiry of the published information relating to other studies where written consent is necessary.

Abbreviations

PD	Pancreaticoduodenectomy
IOF	Intraoperative fluid
TF_POD5	Total amount of fluid given until POD #5
POF	Postoperative fluid
POD	Postoperative day
DGE	Delayed gastric emptying
PPH	Postpancreatectomy hemorrhage
POPF	Postoperative pancreatic fistula
ASA	American Society of Anesthesiologists
ISGPS	International study group pancreatic surgery

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