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ORIGINAL INVESTIGATION

The clinical impact of the systolic volume variation guided intraoperative fluid administration regimen on surgical outcomes after pancreaticoduodenectomy: a retrospective cohort study

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Abstract
Background: Pancreaticoduodenectomy is associated with high morbidity. Many preoperative variables are risk factors for postoperative complications, but they are primarily non-modifiable. It is not clear whether an intraoperative goal-directed fluid regimen might be associated with fewer postoperative surgical complications compared to current conservative, non-goal-directed fluid practices. We hypothesize that the use of Systolic Volume Variation (SVV)-guided intraoperative fluid administration might be beneficial.
Methods: Data from 223 patients who underwent pancreaticoduodenectomy in our institution between 2015 and 2019 were reviewed. Patients were classified into two groups based on the use of intraoperative use of SVV to guide the administration of fluids. The decision to use SVV or not was made by the attending anesthesiologist. Subjects were classified into SVV-guided intraoperative fluid therapy (SVV group) and non-SVV-guided intraoperative fluid therapy (non-SVV group). Uni and multivariate regression analyses were conducted to determine if SVV-guided fluid therapy was significantly associated with a lower incidence of postoperative surgical complications, such as Postoperative Pancreatic Fistula (POPF), Delayed Gastric Emptying (DGE), among others, after adjusting for confounders.

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Results: Baseline, demographic, and intraoperative characteristics were similar between SVV and non-SVV groups. In the multivariate analysis, the use of SVV guidance was significantly associated with fewer postoperative surgical complications (OR = 0.48; 95% CI 0.25−0.91; *p* = 0.025), even after adjusting for significant covariates, such as perioperative use of epidural, pancreatic gland parenchyma texture, and diameter of the pancreatic duct.

Conclusions: VV-guided intraoperative fluid administration might be associated with fewer postoperative surgical complications after pancreaticoduodenectomy.

Introduction

Pancreaticoduodenectomy is associated with many postoperative morbid outcomes. The postoperative complication rate varies from 35% to 58%, and perioperative mortality is around 2−4% in reference centers.[1] Pancreaticoduodenectomy is, however, the standard of treatment for pancreatic and periampullary tumors.[2] Because of its high morbidity, a multidisciplinary approach is mandatory to achieve favorable outcomes.[3]

A regimen of liberal intraoperative fluid administration is known to be associated with higher rates of complications and unfavorable outcomes in colorectal surgery, such as anastomotic leak, since excessive fluid administration is associated with edema and tissue hypoxia.[4] On the other hand, hypovolemic states were reported to be associated with ischemia-related events, such as acute renal failure.[5] In the scenario of pancreatic surgery, it is not clear whether an intraoperative goal-directed fluid regimen is associated with fewer postoperative surgical complications. Results from previous studies are controversial and difficult to compare because the definition of what was considered as a more restrictive or liberal fluid regimen was neither objective, nor individualized.[2,6,7] Moreover, previous studies did not consider the effects of well-known surgical variables, such as pancreatic gland texture and duct size in their analysis.

In recent years, emerging evidence has shown that intraoperative fluid replacement should be guided by more objective measures of real-time perfusion and/or adequate volume status for each individual patient. Since then, the use of Systolic Volume Variation (SVV) has been increasingly implemented due to its simple use, accuracy, and minimal invasiveness.

Although SVV appears to accurately predict fluid responsiveness, its impact on surgical or clinical outcomes remains unclear.[8] The aim of this study is to compare the short-term postoperative outcomes, namely postoperative surgical complications, of patients who received an SVV- or non-SVV-guided fluid regimen intraoperatively to determine the clinical impact of intraoperative SVV guidance on postoperative pancreaticoduodenectomy outcomes.

Methods

This was a retrospective, observational cohort study of patients who underwent pancreaticoduodenectomy in our institution, from 2015 to 2019, using our prospectively managed database. This study was approved by our Ethical Committee (# 51194021.5.0000.5258) and adhered to the STROBE checklist for reporting of cohort studies.

The rationale for SVV predicting responsiveness to a volume challenge is based on changes in Systolic Volume (SV) or pulse pressure during alterations in cardiac preload provoked by positive-pressure mechanical ventilation.[9] Under positive pressure mechanical ventilation, specifically during inspiration, the intrapleural pressure rises and the venous pressure gradient is lowered. This causes a reduction in the patient's Right Ventricular (RV) preload. Additionally, the RV afterload is increased due to an increase in transpulmonary pressure. The result is a reduction in RV Stroke Volume (SV) leading to a reduced Left Ventricular (LV) filling volume.[10] LV output is ultimately reduced after 2−3 subsequent heartbeats, reaching its minimum during the expiratory phase. The amplitude of these changes is greater if the patient is in a low volume status, on the ascending part of Frank Starling's curve. Therefore, SVV can be used to see an arterial swing on an arterial trace suggesting that the patient is in a low volume status and would benefit from more fluids,[9] with the use of the Vigileo/Flo trac (Edwards Lifeciences®) monitor. Even though the algorithms and protocols for the use of SVV may vary depending on institution and clinician preference, most tend to be very similar. In our institution we use the one shown in Figure 1.[11]

The primary outcome measure was the occurrence of any postoperative surgical complication, according to the Clavien-Dindo classification.[12] We also collected perioperative data regarding the type of fluid regimen administered intraoperatively (SVV-guided or non-SVV-guided), and other factors we reasonably assumed could possibly impact the relationship between the regimen of intraoperative fluid administration and our outcomes of interest. These factors included the total amount of intraoperative fluids used, the type of fluid used (crystalloids only or both crystalloids and colloids), intraoperative use of vasopressors, and intraoperative use of epidural analgesia. Intraoperative data regarding the texture of the pancreatic gland parenchyma and pancreatic duct size, since the relationship between pancreatic gland texture/duct size and postoperative surgical complications has been well established, were also collected. Soft pancreatic texture and ductal size of ≤ 3 mm are associated with a higher risk of postoperative complications such as Postoperative Pancreatic Fistula (POPF). Soft pancreas and small ductal size are significantly relevant factors in the Fistula Risk Score (FRS), based on the 2005 and 2016 International Study Group of Pancreatic Fistula classification (ISGPFc).[13,14] Patients with serious cardiovascular or pulmonary diseases were excluded from the study. We also
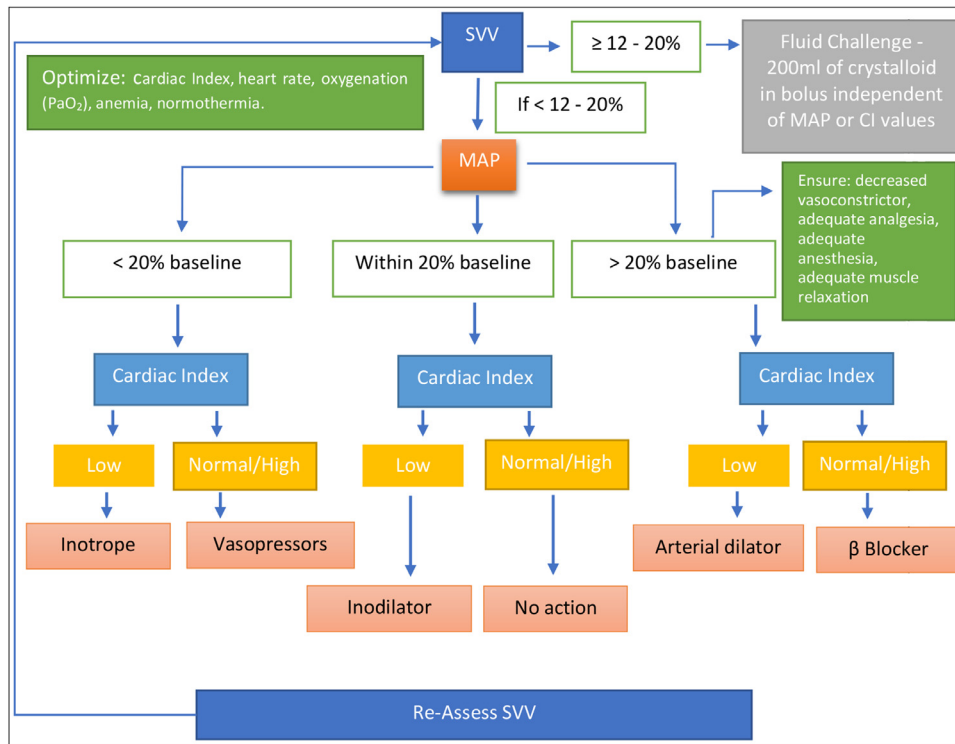
Figure 1 Our Institution's algorithm for intraoperative fluid management guided by SVV and CI using Vigileo/FloTrack (MAP, Mean Arterial Pressure; SVV, Stroke Volume Variation).

collected data regarding demographic characteristics and preoperative diagnosis (Tables 1 and 2).

Patients were first classified into SVV and non-SVV groups. The decision of using or not SVV was made by the attending anesthesiologist. In our institution, high complex surgeries such as pancreaticoduodenectomy have anesthesia care performed by a small number of clinicians, and the use of SVV implies adherence to the protocol described on Figure 1.

The Vigileo/Flo trac (Edwards Lifeciences®) monitor was used on the SVV group. MAP and CI were used only when, based on the values of the SVV, we had no reason to believe that volume challenge wouldn't be beneficial for that specific patient. If so, we used MAP and CI to decide what was the most appropriate care for that patient (Vasopressors, Inodilators). In the non-SVV group, none of those variables were considered to guide intraoperative fluid management.

Table 1 Demografic, preoperative diagnosis and pancreas characteristics of SVV and non-SVV groups.

	SVV (n = 73)		No SVV (n = 150)		Total (n = 223)		p
	n or Mean	% or SD	n or Mean	% or SD	n	%	
Sex							
Female	33	45.21	69	46	102	45.74	0.911
Male	40	54.79	81	54	121	54.26	
Age	66.74	11.32	64.29	12.39			0.156
BMI	25.12	4.78	25.92	5.80			0.35
Pancreatic gland texture							
Hard	35	47.95	66	44	101	45.29	0.579
Soft	38	52.05	84	56	122	54.71	
Pancreatic Duct Size							
< 3 mm	12	16.44	21	14	33	14.8	0.357
3–6 mm	46	63.01	73	48.67	119	53.36	
> 6 mm	15	20.55	56	32.48	71	31.84	
Diagnosis							
Cancer (vs. Benign)	58	79.45	110.00	74.32	168.00	76.02	0.56
NET (vs. Benign)	5	5.48	15	9.46	20	8.14	
Beningn	11	15.07	24	16.22	35	15.84	

Table 2 Intra- and postoperative caracteristics of SVV and non-SVV groups.

	SVV (n = 73)		No SVV (n = 150)		Total (n = 223)		
	n or Mean	% or SD	n or Mean	% or SD	n	%	p
Any Surgical Complications							
Yes	43	57.35	104	72.99	147	67.8	**0.024**
No	34	42.65	42	27.01	76	32.2	
Major Surgical Complications (≥ Grade 3)							
Yes	42	57.53	82	54.67	124	55.61	0.686
No	31	42.47	68	45.33	99	44.39	
Type of Surgical Complication							
DGE	13		45		58		0.719
Fistula	11		28		39		
Other	19		31		50		
Amount of Fluids (mL.KgH)	8.49	2876	7.67	2695			**0.036**
Type of Surgical fluids							
Cristalloids	21.00	28.77	58.00	38.67	79.00	35.43	0.147
Both cristalloids and colloids	52.00	71.23	92.00	61.33	144.00	64.57	
Vasopressors used intraoperatively							
Yes	71.00	97.26	145.00	96.67	216.00	96.86	0.811
No	2.00	2.74	5.00	3.33	7.00	3.14	
Estimated Blood Loss (mL)	420.00	348.33	376.77	233.417			0.273
Perioperative use of epidural							
Yes	59.00	81.94	126.00	84.46	185.00	83.64	0.64
No	14.00	18.06	24.00	15.54	38.00	16.36	
Lengh of Hospital Stay (Days)	123.088	8.639	13.197	7.339			0.443
Lengh of CU Stay (Days)	1.68	2.033	1.445	18.709			0.397
Readmission to ICU in 90 days							
Yes	21.00	26.42	46	29.41	67	28.49	0.688
No	50.00	73.58	106	70.59	156	71.51	
Duration of Surgery (min)	400.70	63479	400.48	91.61			0.985

All the previously mentioned variables were compared between both groups. Following this, both uni and multivariate analyses were conducted to assess factors that were significantly associated with our outcome of interest. For continuous variables, we used unpaired two-sample t-test (two tailed) for group comparison. For categorical variables, we used the chi-square test. For the uni and multivariate analyses, we used logistic regression. For the multivariate analysis, we used forward selection of variables, starting with the one with the lowest p-value on univariate analysis, ending only with the variables with p-values less than 0.05 in the univariate analysis. We had previously estimated a sample size of 140 patients (70 patients in each group) to power the study to detect a difference in any grade postoperative surgical complications of at least 20% between groups (80% power), assuming a type I error (α) of 0.05, accounting for five predictors in a multiple regression model. We used the free online software G-Power® for sample size calculation. We ended up including 223 cases. All analyses were performed using Stata version 15.1 (StataCorp LLC, College Station, Texas, USA).

Results

Baseline demographic and preoperative factors did not have statistical difference between the SVV and non-SVV groups (Table 1). Intraoperative and postoperative factors also did not have statistical difference between groups, except for surgical complications (p = 0.024) and the total amount of fluids given (p = 0.036). Nearly half of the complications on the SVV group consisted of Delayed Gastric Emptying (DGE) and postoperative pancreatic fistula. In the non-SVV group, those two complications comprised nearly two thirds of the total complications. Other postoperative complications, such as bleeding, intra-abdominal collection, among others were individually in small numbers. Thus, we decided to group them as "others". Additionally, estimated blood loss and the use of blood products did not differ between groups (Table 2). The uni and multivariate analyses of factors potentially associated with the occurrence of any postoperative surgical complication are shown in Table 3. In the univariate analyses, the regimen of intraoperative fluid administration (SVV- or non-SVV-guided), perioperative use of epidural, pancreatic gland texture, and pancreatic duct diameter ≤ 3 mm were all associated with postoperative surgical complications. In the multivariate analyses, the use of SVV guidance was significantly associated with fewer postoperative surgical complications (OR = 0.48; 95% CI 0.25−0.91; p = 0.025), along with perioperative use of epidural (OR = 0.33; 95% CI 0.13−0.87; p = 0.025) and hard pancreas (OR = 0.45; 95% CI 0.22−0.89; p = 0.022). The total amount of intraoperative fluid administered was not a relevant factor associated with postoperative surgical complications in either analysis.

Table 3   Uni and multivariate analyses of clinical factors affecting surgical complications.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Male	0.84	0.46–1.51	0.568			
Age > 65	1.53	0.85–2.58	0.156			
BMI > 25	1.31	0.72–2.36	0.378			
Regimen of fluid administration was SVV-guided	0.50	0.27–0.92	**0.025**	0.48	0.25–0.91	**0.025**
Amount of fluids > 8 mL KgH	0.74	0.41–1.33	0.314			
Type of fluids (both cristaloids and colloids)	0.80	0.59–1.09	0.168			
Intraoperative use of vasopressors	3.26	3.26–20.01	0.201			
Estimated blood loss was > 400 mL	0.92	0.51–1.66	0.771			
Perioperative use of epidural	0.38	0.15–0.96	**0.042**	0.33	0.13–0.87	**0.025**
Soft pancreatic gland texture	2.29	1.26–4.17	**0.007**	2.22	1.12–4.40	**0.022**
Pancreatic Duct Size						
< 3 mm (vs. > 6 mm)	0.39	0.16–0.96	**0.041**	0.64	0.23–1.75	0.382
3–6 mm (vs. > 6 mm)	0.68	0.34–1.38	0.283	1.08	0.49–2.41	0.842
> 6 mm	1.00					
Diagnosis		–				
Cancer (vs. Benign)	0.94	0.41–2.12	0.873			
NET (vs. Benign)	1.14	0.29–4.52	0.856			
Benign	1.00					
Duration of sugery > 400 min	0.74	0.41–1.33	0.316			

Discussion

Recently, attention has been focused on intraoperative factors that might impact immediate and long-term postoperative surgical outcomes. The adoption of protocols like that of ERAS by many institutions around the world shows the extent of attention this topic has acquired in the past years.[15] The perioperative use of epidural anesthesia, vasopressor, blood products, total amount of fluid administered, type of fluid used, and, most importantly, the regimen of fluid administration (goal-directed or not), based on patient's real-time individualized needs are all controversial topics in modern intraoperative fluid management.

In our study, we failed to find any significant effects from the use of SVV in clinically relevant postoperative outcomes, such as length of hospital and ICU stay and readmission to the ICU (Table 3). Previous retrospective studies that compared restrictive intraoperative fluid approach and liberal intraoperative fluid approach in pancreaticoduodenectomy also failed to show any significant difference in short term surgical outcomes, such as length of hospital stay, or postoperative surgical complications, such as Postoperative Pancreatic Fistula (POPF), Delayed Gastric Empty (DGE), infections, or hemorrhage.[2,6,16,17] A systematic review of the literature with meta-analysis comparing a restrictive versus liberal intraoperative fluid approach (fixed total amount of fluid administered) found no difference between groups in terms of postoperative surgical complications.[18] The largest known clinical trial (n = 330) that compared different intraoperative fluid regimens and surgical outcomes after pancreaticoduodenectomy also found no difference in the incidence of postoperative surgical complications between patients given restrictive and liberal fluid administration.[19] Our group succeeded in showing a statistically significant difference between SVV and non-SVV groups regarding postoperative surgical complications.

Another group performed a clinical trial comparing the postoperative outcomes of SVV-guided approach and ERAS protocol-guided for intraoperative fluid administration. In this trial, the results for postoperative surgical complications and length of hospital stay favored the SVV group, in which patients received a lower mean total volume of fluid administered.[10] It is important to take note that the ERAS protocol is also supposed to perform intraoperative fluid administration in an individualized manner for every patient.[7] Differently from our study, this group was in fact comparing two different Goal Directed Fluid Therapy (GDFT) strategies.

Gottin et al performed a randomized clinical trial (n = 86), that compared postoperative surgical complications in the SVV-guided group, a restrictive fluid regimen group (< 4 mL.Kg^{-1}.H^{-1}), and a liberal fluid regimen group (> 12 mL.Kg^{-1}.H^{-1}). The results favored both the SVV and the restrictive fluid group.[20] It is important to take note that the total amount of fluids administered in both restrictive and liberal regimen groups in the same study seemed relatively excessive, based on our experience. However, those results coincide with ours.

None of the studies consider the role of other possible covariates in their analysis. Pancreaticoduodenectomy is associated with many postoperative complications, including POPF. Studies have described the texture of the pancreas as an independent predictive factor of the occurrence of POPF and other pancreatic surgery complications.[21] Soft-textured pancreases are associated with a higher incidence of POPF and pancreatic surgery complications[22] and are characterized by increased pancreatic fat and decreased pancreatic fibrosis.[23] Conversely, hard-textured pancreases due to fibrosis are associated with lower POPF formation, as these pancreases allow firmer holding of sutures and tend to have a smaller amount of pancreatic juice secretion. Usually, the assessment of pancreas texture is determined intraoperatively by surgeons although there are only a few

experimental approaches that are not yet fully implemented in clinical practice.[24]

To the best of our knowledge, Andrianello et al were the only authors so far to perform a study that considered the potential role of the pancreatic gland texture in the relationship between fluid regimen and postoperative outcomes. This prospective clinical trial of 350 patients who underwent major pancreatic surgeries compared the difference in POPF incidence between the groups that either received liberal fluid regimen or received fluids based on the ERAS protocol. The incidence of POPF was lower in the ERAS-guided group, suggesting that the use of a strategy for individualized intraoperative fluid administration might, indeed, reduce surgical complications. In the same study, they also stratified patients by the texture of pancreatic gland parenchyma (hard vs. soft). In patients whose pancreases were classified as "soft pancreases", the use of an ERAS-guided approach for intraoperative fluid therapy was associated with a higher incidence of POPF.[25] One could argue that "soft pancreas" itself is already a strong predictor for postoperative surgical complications, so the regimen of intraoperative fluid administration would not matter. Our data indeed show, in the univariate analysis, that "soft pancreas" is associated with more postoperative surgical complications. However, in the multiple logistic regression model, even adjusting for the covariate "soft pancreas", SVV was still associated with fewer postoperative surgical complications.

The literature has also shown that the use of perioperative epidural anesthesia might potentially impact short- and long-term surgical outcomes.[26] We considered that it was reasonable to evaluate whether perioperative use of epidural anesthesia was associated with postoperative surgical complications and could potentially affect the relationship between the regimen of intraoperative fluid administration and postoperative surgical complications. It is important to note that the perioperative use of epidural analgesia did not differ between SVV and non-SVV groups, with 81% of SVV subjects using epidural vs. 84% of non-SVV subjects (Table 2). This difference was considered statistically non-significant. In the univariate logistic regression analysis perioperative use of epidural was, in fact, associated with fewer postoperative surgical complications. For this reason, this important variable was added in a forward step model to the multiple logistic regression equation, and SVV was still associated with fewer postoperative surgical complications, independently of the effects of epidural. We believe that the potential role of perioperative use of epidural and its clinical implications in the context of high-risk pancreatic surgeries deserves more investigation in future studies.

The results of the current study are consistent with the hypothesis that administering intraoperative fluids using SVV guidance is associated with fewer postoperative surgical complications after pancreaticoduodenectomy. It is also interesting to note that the average total amount of fluids administered in the SVV group was significantly higher than that of the non-SVV group. Due to the need for multiple reassessments of intraoperative SVV mentioned in different guidelines, it is our assumption that a higher total volume of intraoperative fluid administration might be a reasonable finding. The literature regarding SVV shows inconsistent results regarding its relationship with the total intraoperative amount of fluids administered.[27]

However, in our study, the total amount of intraoperative fluids administered was not independently associated with postoperative surgical complications in the univariate analyses. This implies the possibility that the method of fluid management (goal-directed or not) is the variable significantly associated with postoperative surgical complications, rather than the total amount of fluid administered. Additionally, the type of fluids used, crystalloids or both crystalloids and colloids, was not associated with postoperative surgical complications.

The difficulty in establishing a causal relationship between the SVV-guided intraoperative fluid regimen and postoperative surgical complications is a potential limitation to our study. Since this is a retrospective study, causality between factors and the outcome of interest could not be defined. Additionally, adherence to protocols constitutes a problem in institutions around the world, and the fact that the clinician responsible for the anesthetic care could not adhere strictly to the protocol showed in Figure 1 should be considered another potential source of bias. Moreover, one could argue that the decision of using SVV, or any other monitor, to improve the quality of anesthetic care by the attending anesthesiologist would imply a different perception of the impact of a more accurate intraoperative anesthetic care in postoperative outcomes, and potentially lead to less postoperative complications. This should also be considered an additional potential source of bias. Even though we certainly must be extremely careful in any analysis and interpretation of the present findings, and the extent of how far we can extrapolate our conclusions based on the present study, our predictive factor was significantly associated with our measured outcome. Consequentially, based on the strength and significance of the evidence we found, future randomized clinical trials on this topic should be performed, especially taking into consideration the role of other potential covariates known to be associated with postoperative surgical complications after pancreaticoduodenectomy.

Based on the data from our institution, we conclude that the use of SVV-guided intraoperative fluid therapy might be associated with fewer minor postoperative surgical complications after pancreaticoduodenectomy, i.e., grade I and II, even after adjusting for factors known to be associated with postoperative surgical complications, such as pancreatic gland parenchyma texture, pancreatic duct size, and perioperative use of epidural anesthesia. Facing the yearly increase in the number of complex surgical procedures, anesthesiologists and surgeons need to be aware of the importance of intraoperative care and its significant relevance to surgical outcomes.

Conflicts of interest

The authors declare no conflicts of interest.

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