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Prospective Randomized Controlled Trial of Liberal versus Restricted Perioperative Fluid Management in Patients Undergoing Pancreatectomy

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Abstract

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Objective—To examine, by a prospective randomized controlled trial, the influence of Liberal (LIB) versus Restricted (RES) perioperative fluid administration on morbidity following pancreatectomy.

Summary Background Data—Randomized controlled trials in patients undergoing major intra-abdominal surgery have challenged the historical use of liberal fluid administration, suggesting a more restricted regimen may be associated with fewer postoperative complications.

Methods—Patients scheduled to undergo pancreatic resection were consented for randomization to a LIB (n=164) or RES (n=166) perioperative fluid regimen. Sample size was designed with 80% power to decrease Grade 3 complications from 35% to 21%.

Results—Between July 2009 and July 2015, we randomized 330 patients undergoing pancreaticoduodenectomy (PD, n=218), central (n=16) or distal pancreatectomy (DP, n=96). Patients were equally distributed for all demographic and intraoperative characteristics. Intraoperatively, LIB patients received crystalloid 12ml/kg/hr and RES patients 6ml/kg/hr. Cumulative crystalloid given (median, range, ml) days 0–3 was LIB: 12252 (6600–21365), RES 7808 (2700–16274) p<0.0001. Sixty day mortality was 2/330 (0.6%). Median operative time for PD was 227 minutes (105–462) and DP 150 (44–323). Grade 3 complications occurred in 20% of LIB and 27% of RES patients (p=0.6). Median length of stay was 7 days and 5 days for PD and DP, respectively, in both arms.

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Conclusions—In a high volume institution, major perioperative complications from pancreatic resection were not significantly influenced by fluid regimens that differed approximately 1.6 fold.

INTRODUCTION

Optimal perioperative fluid management for major intraabdominal operations remains a matter of debate. In the 1950s, Moore and Shires,^{1,2} after initially suggesting that liberal utilization of crystalloid was beneficial in maintaining intravascular volume, revised their recommendations to a more limited replacement regimen. Despite their suggestions, large amounts of fluid continued to be used perioperatively, until others showed increasing complications associated with hypervolemia.^{3–13} In the 2000s, a number of randomized trials demonstrated a positive association between liberal fluid management and postoperative complications in colorectal surgery and other intraabdominal operations.^{5,6,14–20} However, not all studies supported the restricted approach and some found fluid restriction to be harmful.^{21–23} The majority of these studies did not include a significant number of pancreatic resections.

Our previous randomized trial of hemodilution²⁴ suggested that in patients undergoing pancreatic resection, the increased fluid administration required for hemodilution was associated with increased perioperative complications, specifically of the pancreatic anastomosis. This was also addressed more recently in a fluid trial using hypertonic saline in the restricted arm.²⁰ However, two retrospective reviews of fluid management in patients undergoing pancreatectomy did not demonstrate a clinically significant association between postoperative morbidity and intraoperative fluid administration.^{25,26} In an effort to definitively address this question we conducted a prospective randomized trial of Liberal (LIB) versus Restricted (RES) fluid administration for patients undergoing elective pancreatectomy.

MATERIALS AND METHODS

This single center, prospective, randomized, controlled trial was approved by the Institutional Review Board. Patients 18 years of age or older, scheduled for pancreaticoduodenectomy (PD), central or distal pancreatectomy (DP) who met eligibility requirements were approached for participation. Patient exclusions included: participation in a competing trial, pregnancy, history of coronary disease (unless cleared by a negative cardiac stress test), myocardial infarction within 3 months, history of stroke, congestive heart failure (ejection fraction less than 35%), history of severe chronic obstructive pulmonary disease (resting oxygen saturation < 90%), renal dysfunction (creatinine > 1.8 mg/dL), abnormal coagulation parameters (INR > 1.5 not on warfarin, platelet count < 100 K/mcL), active infection, body mass index (BMI) > 35, American Society of Anesthesiologists (ASA) status >3, corticosteroid use equivalent to > 10 mg prednisone/day or bilirubin level > 10mg/dL. Patients with a BMI > 35 were initially stratified but subsequently excluded because of the high volume crystalloid required, based on body weight. When it was noted that patients on the LIB arm had received over 1200ml/hr crystalloid and were diuresing sufficiently intraoperatively to meet criteria for decreasing the IV rate, the decision was made to exclude high BMI patients to keep the ml/kg/hr uniform.

Preoperative and Intraoperative Management

All patients underwent a complete history and physical examination preoperatively, including formal medical evaluation when needed. Radiographic studies were reviewed to minimize the possibility of local unresectability or metastatic disease. No patients received preoperative mechanical bowel preparation. All patients had baseline weights documented preoperatively.

Eligible patients who were not registered to another trial were approached by a consenting professional (anesthesiologist or surgeon) on the morning of surgery for participation in the trial. Consented patients were brought to the operating room where standard monitors were placed. Most patients arrived with an indwelling 18g intravenous catheter (IV). After standard anesthetic induction, an additional large bore IV was placed, as well as an arterial line in cases of PD. Antibiotic prophylaxis consisted of a single intraoperative dose in all patients prior to surgical incision. One surgeon used octreotide perioperatively until October 2014, when the use of pasireotide was adopted by all surgeons.²⁷ No epidural catheters were used in this study. All patients were initially started with fluid administration as outlined in the RES Arm until resectability was determined by the operating surgeon. At that point a sequentially numbered opaque envelope generated by the Biostatistics Department and kept in a designated drawer was retrieved by the Anesthesiologist and the patient was randomized to either the LIB or RES Arm. Patients randomized to the LIB Arm were given additional fluids as described below.

Restricted Arm

The RES Arm patients received maintenance intravenous crystalloid (Normosol, Hospira, Inc., Lake Forrest, Ill) at 6ml/kg/hr. Blood loss was replaced ml: ml with 5% albumin until transfusion criteria (hemoglobin (Hb) < 8mg/dL) were met. Additional fluid boluses of 100ml Normosol or bolus pressors (phenylephrine or ephedrine) were used to maintain hemodynamic stability. Fluid boluses of 250ml Normosol were given for urine output less than 0.5 ml/kg for 2 hours. For later starting cases, an additional bolus of Normosol of 0.5 ml/kg was given for each fasted hour from 8AM until induction.

Liberal Arm

At randomization to the LIB Arm, additional Normosol was given to bring the maintenance fluids to 12ml/kg/hr. Blood loss was similarly replaced as in the RES Arm, as well as additional fluid boluses. Normosol 250ml boluses were used to maintain urine output at >1ml/kg for 2 hours. For later starting cases, an additional bolus of Normosol of 1.5 ml/kg/ fasted hour from 8AM was given to bring the total Normosol to 2ml/kg/ fasted hour.

The pancreaticoduodenectomy patients received either a standard Whipple procedure or a pylorus preserving pancreaticoduodenectomy. The pancreatic reconstruction was typically performed to a single loop duct to mucosa pancreaticojejunostomy, in 2 layers. The gastrojejunostomy was an ante colic loop, end to side, in two layers with running absorbable sutures.

The distal procedures were done open (n=77), laparoscopically (n=11) or robotically (n=8).

Abdominal drains and nasogastric tubes were used at the discretion of the operating surgeon. Patients were awakened and extubated at the end of the procedure and transferred to the Post Anesthesia Care Unit (PACU).

POD 0 (PACU) Management

All patients had strict inputs and outputs measured. Patients undergoing pancreaticoduodenectomy were observed in the PACU overnight, then transferred to the inpatient floor the next morning if stable. Patients undergoing other procedures were similarly transferred with or without an overnight stay. All patients received postoperative patient controlled analgesia (PCA). IV acetaminophen was used at the surgeon's discretion.

Patients on the RES Arm received Normosol or an equivalent crystalloid solution at a rate of 60ml/hr. Urine output was maintained at >40ml/2 hrs with boluses of 250ml of a crystalloid solution. Fluid boluses were administered to maintain hemodynamic stability as needed. Medications were mixed as per pharmacy protocol, and volume administered included in the daily input.

Patients on the LIB Arm received Normosol or equivalent at a rate of 125ml/hr (100ml/hr for those weighing <50kg.) Urine output was maintained at 0.5ml/kg/hr with crystalloid boluses of 250ml. Fluid boluses and pharmacy medications were included as above.

POD 1 and thereafter

RES Arm patients received D5W/0.5%NS with 20mEqKCl/L or equivalent solution at 50ml/hr until their oral intake was > 500ml/24 hrs. Urine output was maintained at 160ml/8 hrs with crystalloid boluses of 250ml.

LIB Arm patients received the same at 100ml/hr until their oral intake was >500ml/24 hrs. Urine output was maintained at 240ml/8 hrs (pretrial standard) with crystalloid boluses of 250ml. If the urine output increased to greater than 80ml/hr over 8 hours, or the patient appeared clinically volume overloaded, the IV rate was decreased. Furosemide was used at the discretion of the attending surgeon.

DATA COLLECTION AND STUDY ENDPOINTS

Demographic, laboratory, intraoperative and postoperative fluid data, weights, disease and treatment related variables (presence of a preoperative stent, length of procedure, use of drains, pancreatic gland and duct data, pathology), postoperative milestones (day of ambulation, oral intake >500ml, day of IV rate reduction to KVO, Foley catheter removal, flatus, solid intake, bowel movement, date of discharge and perioperative complications) were recorded prospectively. Post discharge complications were collected for 90 days from the hospital reporting system which captured all patients either readmitted to the hospital or seen in our Urgent Care Center. Treatments which occurred outside of our institution were uploaded to our electronic medical record and also recorded.

Complications were graded in severity using the modified Dindo, Clavien classification of surgical complications.^{28,29} This classification grades complications from 1–5, with Grade 1

complications requiring bedside intervention. Grade 2 require moderate interventions, such as intravenous medications. Grade 3 require either a surgical, endoscopic or interventional radiology (IR) procedure for treatment. Grade 4 result in chronic deficit or disability. Grade 5 complications result in death.

The primary endpoint was defined as the prevalence of postoperative Grade 3 complications within 60 days. Pancreas specific complications such as collections, abscesses or fistulas were grouped together as only 20% of patients received drains making the ISGPS definitions inapplicable. Our drain use has decreased since we showed an association with longer hospital stay and more Grade 3 complications.^{30, 31}

Secondary endpoints included length of stay (LOS) and delayed gastric emptying (DGE), using the ISGPS definition,^{29,32} although nasogastric tubes were rarely used beyond POD 0. The incidence of other morbidity (Grades <3 and >3) was also recorded.

STATISTICAL ANALYSIS

The primary objective of this study was to determine if RES perioperative fluid management decreases the incidence of Grade 3 or higher postoperative complications in adults undergoing pancreatic resection. Three hundred thirty patients were 1:1 randomized to the treatment arms intraoperatively using opaque envelopes generated by the Biostatistics department. Intraoperative randomization was performed after resectability was established. Randomization was performed using permuted blocks of size 8. This sample size provided at least 80% power to distinguish between Grade 3 complication rates of 21% and 35% (Type I error of 5%, chi-square test). It also allowed for two interim analyses for potentially stopping the trial early both for futility and safety. The 35% complication rate was based on our prior retrospective analysis²⁵ and comparable historical reports in the literature. Primary analysis was based on the intent-to-treat principle. The primary outcome of major complications was compared using a chi-square test. Secondary outcomes were compared using a Wilcoxon test (length of stay, creatinine values and fluid administration) or Fisher's exact test (use of octreotide or pasireotide, intraoperative drain placement, pancreatic consistency). The effect size for the primary endpoint and all secondary endpoints were reported as a risk ratio along with 95% confidence intervals.

RESULTS

From July 2009 through July 2015, 393 patients scheduled for pancreatic resection were registered to the study. Resectability was established in 330; 164 patients randomized to LIB Arm and 166 patients randomized to RES Arm (Figure 1). Two interim analyses took place when accrual met 150 and 300 to assess for harm or futility. All randomized patients received the intended treatment and were analyzed for the primary and secondary outcomes. No losses or exclusions occurred after randomization. The trial was ended when target accrual was achieved.

Patient demographics are shown in Table 1 and confirm no clinically meaningful differences between the preoperative parameters including age, BMI, diagnosis and preoperative biliary stenting. Weight was higher in the RES group ($p=0.02$). No statistically significant

differences were identified between the two arms in procedure, length of operation, use of octreotide or pasireotide, intraoperative drain placement, pancreatic consistency or pancreatic duct size (Table 2). Grade 3 complications were greater in the presence of a soft gland 30/54 (55%) than in a hard gland 24/54 (44%) but not different between the LIB and RES arms.

Postoperative days 1, 2 and 3 showed statistically different creatinine values, which were not clinically relevant and normalized by POD 4 (medians not different). Three patients on the LIB arm and four patients on the RES arm developed increases in creatinine high enough to meet the CTCAE criteria for a Grade 1 injury.³³ One patient in each arm developed Grade 4 renal failure.

The fluid administration for each treatment arm by intention to treat is described in Table 3. An increase in crystalloid utilization on day 0 was 77% greater in the LIB Arm, on day 1, 79%, and day 2, 56%. By Day 3 both groups received similar fluid intake, as 10–20% of the DP patients were no longer receiving IV fluids. By day 4 most of the patients in the LIB arm had their fluid rates decreased. Patients in the RES Arm received significantly more fluid boluses during POD 0, accounted for by administration in the OR only ($p=0.001$). For the period Days 0–4, transfusion rates were 14% LIB and 8% RES $p=0.12$. The combined crystalloid use was in a ratio of LIB: RES 1.63 for Days 0–2 and 1.57 for days 0–3.

Table 4 describes the % complications by Grade between the groups. Overall in hospital and 60 day mortality (Grade 5) was 2/330 or 0.6%. In both groups the expected Grade 3 complication rate of 35% was reduced to 20% (LIB) and 27% (RES) $p = 0.6$ (RR 0.76, 95%CI 0.51–1.12). There was no difference in Grade 3 intraabdominal fluid collections/abscesses (10%, 34/330, RR 0.80, 95%CI 0.42–1.52) or pancreatic/biliary leaks/fistulae (6%, 20/330, RR 0.74, 95%CI 0.30–1.78), between groups (Table 5).

Of the pancreas specific complications, we found Grade 3 complications in the LIB arm of 15% and RES, 18%. When we analyzed the pancreaticoduodenectomy resections separately, we again found no difference in Grade 3 complications between the LIB and RES groups. ($p=0.77$). In the distal resections we also looked at the impact of minimally invasive procedures, 11 in the LIB arm and 8 in the RES arm, but also found similar proportions of Grade 3 complications, none significant.

There were 7 cases of arrhythmias and 4 pulmonary complications in the RES group and 8 arrhythmias and 5 pulmonary complications in the LIB group, similar to our previous report.^{25,29}

We also found no difference in the secondary endpoint of LOS. We improved LOS with time in both groups compared with the period 2004 – 2009 where median stay was 8 days (1–68) without complications and 12 days (1–252) in those with complications Grade 3 or greater²⁵ (Table 5). In the present study, patients without complications had a median stay of 6 days in both groups and with complications Grade 3 or greater had a median of 8 days (5–48) LIB and 9 days (4–34) in RES ($p=0.6$).

The DGE rate was decreased to 4.9% in the LIB arm and 3.6% in the RES arm ($p=0.6$, RR 1.35, 95% CI 0.48–3.80, [Table 5]), as compared with 7% previously.^{25,29}

There were 3 reoperations in the LIB group and 2 in the RES group ($p=0.68$). Twenty six (16%) patients required IR intervention in the LIB group and 41 (25%) in the RES ($p=0.06$). Readmissions within 30 and 60 days were greater in the RES group. No other statistically significant findings between groups were found (Table 5).

DISCUSSION

In order to definitively address the ongoing debate on the optimal perioperative fluid management in patients undergoing major intraabdominal surgery, we successfully completed a prospective randomized controlled trial in 330 patients looking at the impact of two fluid management protocols on the complication rate after pancreatic resection. Previous authors have found mixed results; however, few trials have focused purely on pancreatic resection.²⁰ Our previous retrospective analysis of 1030 patients²⁵ did not show a difference in the Grade 3 complication rate which prompted the current trial.

In this trial we compared two perioperative crystalloid regimens using Normosol, described above as the perioperative solution. Normosol (our institutional standard) is a balanced salt solution, equivalent in electrolyte composition to Isolyte and Plasmalyte, and differs from Ringers Lactate mainly in the absence of calcium and lactate and presence of acetate and gluconate.

We found no statistical difference in the rate of Grade 3 complications following pancreatic resection in patients in either the LIB or RES groups. We report a Grade 3 complication rate of 20% in the LIB and 27% in the RES arm, both less than the prior complication rate of 35% we have previously reported²⁹ on which our statistical power computation and sample size were calculated. This relationship held for proximal and distal resections as well as minimally invasive procedures.

There was a statistically significant, although not clinically relevant increase seen in creatinine levels. Three patients on the LIB arm and four patients on the RES arm sustained rises in creatinine 1.5–2 times baseline, 5 of which normalized by POD 4. Two patients developed chronic renal failure, 1 patient in each arm. Both of these patients' renal morbidity was preceded by a Grade 3 pancreatic leak or intraabdominal collection.

Between days 0–4 we also saw a transfusion rate of 14% in patients on the LIB Arm, versus 8% on the RES Arm, perhaps related to perioperative hemodilution as the starting hemoglobin values were not significantly different. The DGE rate was decreased to 4.9% in the LIB arm and 3.6% in the RES arm, as compared with 7% previously.^{25,29} Mortality in both arms was the same, with a composite rate of 0.6%.

We found no difference in complication rate between the LIB and RES groups. In our hemodilution (HD) RCT in which the HD group received more fluid than the LIB Arm of the present trial, there was a trend towards increased complications in that arm.²⁴ One reason for the lack of detectable difference in the current study may be that our historical leak rate

for distal and proximal pancreatectomy is 35%, which formed the statistical basis for our power calculation.^{24,25} The decreased complication rates in both arms of the current study compared with historical controls very likely limited the ability to find statistically significant differences.

Another possible reason for the failure to document an outcome difference may have been that our criteria were too stringent in choosing our fluid rates. We based our rate for the LIB Arm on the literature and local current practice at the time we initiated the study.⁵ We were able to maintain the ratio of fluids at 1.5 to 2 fold throughout POD3, after which many patients had their IV rates minimized. We found that most patients on the LIB Arm appeared to be well if not over hydrated based on BUN, Cr and urine output. We did build in a fluid cap if urine output exceeded the equivalent of 80ml/hr over several hours, which occurred in many patients on the LIB Arm.

We based the rate of the RES Arm on our previous trials of conservative fluid management and the low CVP technique developed for liver resection at our institution.³⁴ Within the range of fluid management described above, there is no difference in complications or LOS in either group.

There are several limitations of the current study that must be acknowledged. First, this was a single institution study, and although MSKCC is a high volume center,³⁵ generalizability of the results is not a given.

In addition, the attending surgical investigators were not blinded to the randomization. However, due to the relatively moderate amounts of fluids used in the Liberal Arm, no patients were visibly edematous postoperatively. Urine output could be a clue to some patients on the Liberal Arm, although all fluid and complication data was collected by one anesthesiologist and research assistant and then compared with the complication data base entered independently into the medical record by the surgical service. Since the patients on the Liberal Arm required greater urine output as per protocol, patients on both arms received comparable fluid boluses. No infusions of pressors required perioperatively were limited to the Restricted Arm, rather, pressor dependent patients were those having complications and occurred equally in either group. The only statistically significant difference was in several patients on the Restricted Arm who received more boluses in the OR.

Also, we included distal as well as proximal resections as we were primarily focused on postoperative leaks/collections from which distal pancreatectomies are not immune. When we compared proximal versus distal resections, and distal versus minimally invasive resections, we still found no statistical difference in Grade 3 complications.

Finally, we did not use such physiologic measures as degree of tissue edema or tissue oxygen tension nor did we follow a goal directed fluid management protocol. At the time this study was initiated, these devices were not available for routine clinical use. As they became available, we used them during proximal pancreatectomies but only to collect data and chose to not change the study design. These data will be evaluated and reported separately.

These are difficult trials to conduct as many practitioners have been trained to give fluids to maintain a high urine output. The practice of giving excess fluid followed by diuretics is also a common approach. The goal is immediate normalization of all measurable blood levels, rather than the acceptance that given normal renal function, the kidney will correct to normality, albeit less rapidly, than that forced by fluid and drug induced change.

Conclusions

This trial represents a definitive analysis of the effect of moderate degrees of liberal and restricted fluid management on the complication rate after pancreatic resection. We believe that there is enough data, from our study and that of others, to comfortably address the issue of fluid management. In a high volume center, with minimal mortality and progressively recognized and treated morbidity to lower rates than historical norms, complication rates are not significantly altered by regimens of perioperative fluid management that differ by 1.5 to 2 fold.

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Figure 1.
Patient Randomization Flowchart

Table 1

Patient Characteristics By Treatment Arm - median (range)

	Liberal (n=164)	Restricted (n=166)	p
Age (yrs)	65 (29–85)	65 (24–86)	0.38
Sex, n (%)			0.05
Male	77 (47)	97 (58)	
Female	87 (53)	69 (42)	
BMI kg/m ²	26.7 (16.1–39.5)	26.5 (17.6–38.4)	0.22
Weight (kg)	70.6 (43.1–109)	75.4 (45.4–118)	0.02
Histologic Diagnosis, n (%)			0.03
Adenocarcinoma	96 (58)	104 (63)	
NET	24 (15)	13 (8)	
IPMN	12 (7)	24 (14)	
Other Malignant	6 (4)	9 (5)	
Other Benign	26 (16)	16 (10)	
Preop Biliary Stent, n (%)			0.65
Yes	56 (34)	61 (37)	
No	108 (66)	105 (63)	
ASA Status (%)			0.92
1	6 (4)	7 (4)	
2	90 (55)	88 (53)	
3	68 (41)	71 (43)	

ASA-American society of anesthesiologist; BMI-Body Mass Index; NET, Neuroendocrine Tumor; IPMN Intraductal Papillary Mucinous Neoplasm

Table 2

Intervention and Gland Characteristics By Treatment Arm - median (range)

	Liberal n=164	Restricted n=166	p
Procedure, n (%)			0.86
Pancreaticoduodenectomy	107 (65)	111 (67)	
Distal	48 (29)	48 (29)	
Central	9 (6)	7 (4)	
Length of Operation (minutes)			
All	197 (44–379)	206 (68–462)	0.20
Pancreaticoduodenectomy *	215 (97–379) n=116	229 (87–462) n=118	0.40
Distal	136 (44–310) n=48	157 (68–323) n=48	0.16
Octreotide, n (%)			0.86
Yes	16 (10)	18 (11)	
No	148 (90)	148 (89)	
Pasireotide, n (%)			1.0
Yes	37 (23)	37 (22)	
No	127 (77)	129 (78)	
Intraoperative Drain, n (%)			0.16
Yes	33 (20)	45 (27)	
No	131 (80)	121 (73)	
Pancreatic Consistency, n (%)			0.74
Soft	96 (59)	93 (56)	
Hard	68 (41)	73 (44)	
Pancreatic Duct Size, n (%)			0.69
4mm	82 (50)	81 (49)	
5–8mm	69 (42)	75 (45)	
>8mm	13 (8)	10 (6)	

* Includes all central pancreatectomies

Table 3

Fluid Intake By Day By Treatment Arm (ml) - median(range)

	Liberal n=164	Restricted n=166	p
Intraoperative			
-Crystalloid	3563 (1050–7550) (100%)	2050 (650–5130) (100%)	<.0001
-Albumin	363 (0–4000) (85%)	390 (0–2500) (92%)	0.37
-RBC	0 (0–1050) (4%)	0 (0–1750) (1%)	0.06
-FFP	0 (0–577) (2%)	0 (0–884) (2%)	0.99
PACU			
-Crystalloid	2151 (1030–4856) (100%)	1178 (550–4791) (100%)	<.0001
-Albumin	0 (0–750) (2%)	0 (0–1250) (1%)	0.41
-RBC	0 (0–1050) (5%)	0 (0–1400) (1%)	0.05
-FFP	0 (0–958) (1%)	0 (0–675) (1%)	0.56
Day 1			
-Crystalloid	2577 (1650–6500) (100%)	1436 (1000–4245) (99%)	<.0001
-Albumin	0 (0–500) (2%)	0 (0–1000) (2%)	0.70
-RBC	0 (0–900) (1%)	0 (0–700) (3%)	0.11
-FFP	0 (0–0)	0 (0–1035) (1%)	0.32
Day 2			
-Crystalloid	2494 (480–4924) (99%)	1594 (1017–4169) (99%)	<.0001
-Albumin	0 (0–500) (1%)	0 (0–500) (1%)	0.58
-RBC	0 (0–700) (2%)	0 (0–800) (2%)	0.72
-FFP	0 (0–860) (1%)	0 (0–0)	0.31
Day 3			
-Crystalloid	1589 (280–5770) (79%)	1369 (50–2944) (90%)	0.004
-Albumin	0 (0–0)	0 (0–0)	1
-RBC	0 (0–900) (2%)	0 (0–900) (2%)	0.55
-FFP	0 (0–0)	0 (0–0)	1
Day 4			
-Crystalloid	1385 (140–4700) (37%)	1272 (50–3654) (56%)	0.05
-Albumin	0 (0–250) (1%)	0 (0–0)	0.21
-RBC	0 (0–900) (2%)	0 (0–350) (1%)	0.14
-FFP	0 (0–0)	0 (0–0)	1

- All percentages are based on the n value of each group

Table 4

Complications by Grade (All Procedures)– n (%) * (Total Number of Complications)

	Liberal n=164	Restricted n=166	Risk Ratio (95% CI)	p
Complications				
Grade 1	18 (11%) (19)	12 (7%) (13)	1.51 (0.76–3.05)	1.0
Grade 2	43 (26%) (60)	42 (25%) (56)	1.04 (0.72–1.49)	0.9
Grade 3	33 (20%) (42)	44 (27%) (56)	0.76 (0.51–1.12)	0.6
Grade 4	1 (1%) (1)	1 (1%) (1)	----	----
Grade 5	1 (1%) (1)	1 (1%) (1)	----	----
Major Complications	35 (21.3%)	46 (27.7%)	0.77 (0.53–1.13)	

* Percentage of patients in each arm

Table 5

Selected Complications – n (%)

	Liberal n=164	Restricted n=166	Risk Ratio (95%CI)	p
Grade 3 Complications				
Intraabdominal Fluid Collection/Abscess	15 (9%)	19 (11%)	0.80 (0.42–1.52)	0.6
Pancreatic Leak/Fistula	8 (5%)	11 (7%)	0.74 (0.30 – 1.78)	0.6
Biliary Leak	1 (1%)	0 (0%)	---	0.5
Total	24 (15%)	30 (18%)	0.81 (0.50 – 1.32)	0.5
Grades 2 and 3 Complications				
Intraabdominal Fluid Collection/Abscess	22 (13%)	28 (17%)	0.80 (0.48 – 1.33)	0.5
Pancreatic Leak/Fistula	8 (5%)	12 (7%)	0.67 (0.28 – 1.61)	0.6
Biliary Leak	1 (1%)	1 (1%)	---	1.0
Total	31 (19%)	41 (25%)	0.77 (0.51 – 1.16)	0.2
Occurrence of DGE	8 (4.9%)	6 (3.6%)	1.35 (0.48 – 3.80)	0.6
Return to OR	3 (2%)	2 (1%)	---	0.7
IR Interventions	26 (16%)	41 (25%)	0.64 (0.41 – 1.01)	0.06
Length of Stay - Days				
All	7 (3–57)	7 (3–34)	---	0.32
Pancreaticoduodenectomy *	7 (4–57) n=116	7 (5–34) n=118	---	0.88
Distal	5 (3–34) n=48	5.5 (3–21) n=48	---	0.13
Readmission				
Within 30 Days	24 (15%)	40 (24%)	0.63 (0.34 – 1.16)	0.04
Within 60 Days	31 (19%)	46 (28%)		0.07

* Includes Central Pancreatectomy procedures