World J Surg (2018) 42:2938–2950
https://doi.org/10.1007/s00268-018-4545-6

SCIENTIFIC REVIEW

Systematic Review and Meta-analysis of Restrictive Perioperative Fluid Management in Pancreaticoduodenectomy

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Published online: 20 February 2018

Abstract

Background There is significant interest and controversy surrounding the effect of restrictive fluid management on outcomes in major gastrointestinal surgery. This has been most studied in colorectal surgery, although the literature relating to pancreaticoduodenectomy (PD) patients is growing. The aim of this paper was to generate a comprehensive review of the available evidence for restrictive perioperative fluid management strategies and outcomes in PD.

Methods MEDLINE/PubMed, Embase, and the Cochrane Library were searched from inception to April 2017. A review protocol was utilized and registered with PROSPERO. Primary citations that evaluated perioperative fluid management in PD, including those as part of a clinical pathway, were considered. The primary outcome was postoperative pancreatic fistula (POPF). Secondary outcomes included delayed gastric emptying (DGE), complication rate, length of stay (LOS), mortality, and readmission.

Results A total of six studies involving 846 patients were included (2009–2015), of which four were RCTs. Pooled analysis of RCTs and high-quality observational studies found no effect of restrictive intraoperative fluid management on POPF, DGE, complication rate, LOS, mortality, and readmission. Only one study assessed postoperative fluid management exclusively and found prolonged LOS in patients in the restricted fluid group.

Conclusion Based on results of RCTs and high-quality observational studies, intraoperative fluid restriction in PD has not been shown to significantly affect postoperative outcomes. There are too few studies assessing postoperative fluid management to draw conclusions at this time.

Introduction

Pancreaticoduodenectomy (PD) has historically been associated with high morbidity and mortality. While perioperative outcomes have improved significantly in recent years owing to improvements in surgical technique, anesthesia, interventional radiology, and critical care, the morbidity following PD remains high, with up to 47% of patient experiencing postoperative complications [1–7]. Postoperative complications after PD are associated with a delay in time to adjuvant therapy for malignant etiologies, shorter overall survival, increased risk of readmission, and substantially increased health care costs [8–12]. In large

This work was presented at the American College of Surgeons Clinical Congress, Washington, DC, October 18, 2016.

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part, morbidity after PD is driven by the development of a clinically relevant postoperative pancreatic fistula (POPF) [6]. Overall, 10–15% of patients develop POPF after pancreaticoduodenectomy [2, 6]. Thus, interventions aimed at improving short-term postoperative outcomes in PD are of great interest. While initial studies evaluating the efficacy of perioperative fluid restriction comprised largely of colorectal surgery patients, the body of the literature for other procedures, including PD, is growing [13–16].

The challenge in perioperative fluid management lies in finding the optimal volume status to minimize morbidity. While extensive hypovolemia may lead to tissue damage and organ failure [17], excess fluids can result in poor intestinal anastomotic healing and increased postoperative complications [18–21]. Early studies of intravenous fluid (IVF) administration demonstrated significant benefit with liberal use of IVF, and excess fluids were thought to be renally excreted with no adverse effects [22]. In 2002, a small randomized trial reported delayed return of gastrointestinal function and increased length of stay in patients with excess water and salt balance [23]. This study paved the way for a series of trials assessing the impact of restrictive perioperative fluid management in surgical patients. While some subsequent trials supported the original findings, demonstrating a reduction in postoperative complications and length of stay (LOS) in patients managed with a restrictive fluid regimen [24, 25], other studies failed to reproduce the benefits of fluid restriction on postoperative outcomes [26–29] and some even demonstrated harm [30]. A meta-analysis of randomized trials pertaining to colorectal surgery reported decreased complication rates with fluid restriction, but no effect on mortality and LOS was established [31]. Another meta-analysis that included all patients undergoing abdominal surgery found no difference between restrictive and standard fluid management in complication rates and LOS [32]. Lobo et al. [33] further suggested that both too little and excess fluid administration are detrimental and optimal fluid management should aim for a net fluid balance of zero. These publications have generated interest as well as fueled controversy in perioperative fluid management. Currently, there remains significant variation in opinions and practice regarding perioperative fluid management in abdominal surgery [34].

The aim of this systematic review and meta-analysis was to synthesize current evidence comparing restrictive and standard perioperative fluid management in patients undergoing PD for any indication.

Materials and methods

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [35] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guideline [36]. A protocol was devised prospectively and registered with PROSPERO (CRD42016033202).

Search strategy and study selection

Studies were identified through a comprehensive search strategy that was devised by an experienced information specialist (Appendix 1). A combination of medical subject headings (MeSH) and relevant keywords were used to search Ovid MEDLINE, Ovid Embase, and the Cochrane Library for citations published between 1946 and present. The last search was performed on April 11, 2017. No language restriction was applied.

Citations were first screened for inclusion by titles and abstracts. Full texts of the remaining citations were then screened to generate a list of included studies. Both levels of screening were independently performed by two reviewers (BPC, MC). Disagreements among reviewers were resolved by the senior author (GM). Reference lists of included studies were manually screened for missing citations.

Eligibility criteria

Studies that examined perioperative intravenous fluid restriction strategies in patients undergoing PD were included if they reported at least one of the following outcomes of interest: POPF, delayed gastric emptying (DGE), LOS overall complications, mortality (in-hospital, 30 or 90 days), and hospital readmission. Manuscripts that included fluid restriction as part of a clinical enhanced recovery after surgery (ERAS) pathway were also included if they met other inclusion criteria. If the study population consisted of patients undergoing a variety of procedures including PD, the authors were contacted to obtain data specific to PD patients. There were no limitations on patient age, indication for surgery, or technical aspects of PD (e.g., pylorus-preserving, standard). Conference abstracts which were not published in manuscript format were considered if other inclusion criteria were met. Studies that did not provide quantitative data for fluid administration/balance and outcomes of interest were excluded. Other exclusion criteria included case control studies, non-human studies, lack of control group (case reports, case series), poor study quality as determined by

risk of bias assessment, and other article types (reviews, editorials, commentaries, letters).

Risk of bias assessment

Risk of bias and study quality within included studies was assessed by two reviewers (BPC, MC), and disagreements were resolved by consensus. Randomized controlled trials (RCTs) were assessed using The Cochrane Collaboration's tool for assessing risk of bias [37], while observational studies were assessed using the Methodological Index for Non-Randomized Studies (MINORS) [38]. A MINORS score $\geq$17 was considered high quality as previously published [39]. Studies not meeting this threshold were excluded.

Data extraction

Relevant data were extracted by one reviewer (BPC) and checked for accuracy by a second reviewer (MC). Discrepancies were resolved by consensus. The following information was extracted from each included study: country of origin, date of publication, study design, study objective, dates of included data, patient and surgical details (including age, gender, indication for surgery, type of surgery), types of fluid administered, method of grading complications, outcomes of interest, whether the study assessed fluid administration or balance and whether intraoperative or postoperative fluid management was assessed. Authors of articles that only provided data in graphical format were contacted to obtain numerical data.

Data analysis

Data from included studies are included in summary tables and figures. Review outcomes were synthesized narratively. RCTs and high-quality observational studies were included for meta-analysis, which was performed using Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK). Dichotomous variables were analyzed using the Mantel–Haenszel method and reported with odd ratios (OR) and 95% confidence interval (CI). Continuous variables were analyzed using the inverse variance method and reported with mean differences (MD) and 95% CI. For studies that reported LOS with median and range, mean and standard deviation were estimated using published methods [40]. All analyses were first performed using fixed effects models. Study heterogeneity was assessed using the I^2 statistic: <25% was considered low, 25–50% was considered moderate, and >50% was considered high statistical heterogeneity [41]. In cases of high statistical heterogeneity, a random-effect model was used. $P < 0.05$ was considered significant in all analyses.

Results

After duplicate entries were removed, the literature search yielded 865 citations. Following the two-staged screening process described above, six full-text articles were included (Fig. 1). MINORS score of excluded observational studies ranged from 8 to 16 ($n = 10$ studies).

Characteristics of included studies

The studies include four RCTs [42–45] and two observational studies [46, 47]. All studies were published in English between 2009 and 2015. Multiple attempts were made to contact the authors of one study to obtain graphical data in numerical form, but the study authors did not respond to our requests [47].

Study characteristics are presented in Table 1. A total of 846 patients underwent PD between 2004 and 2013. The mean age was 64.7 years (5 studies), and 58.9% of patients were male (5 studies). Indications for surgery included cancers of the pancreatic head and periampullary or biliary region, duodenal cancer, pancreatic neuroendocrine tumors, unspecified non-pancreatic cancer, and pancreatitis. The type of crystalloids used includes Ringer's Lactate, 0.9% saline with 5% glucose, and Normosol ("isotonic electrolyte solution similar in composition to Lactated Ringer's") [42].

The definition of both restrictive and standard fluid management used in this review is presented in Table 2. Risk of bias assessments within included studies is presented in Table 3. Among the RCTs, fluid restriction interventions occurred intraoperatively in two trials [42, 44] both intra- and postoperatively in one trial [43], and postoperatively in one trial [45]. Among the observational studies, both assessed intraoperative fluids only [46, 47].

Intraoperative fluid management

Pancreatic fistula

POPF was reported as an outcome of interest in five studies [42–44, 46, 47], four of which used the International Study Group for Pancreatic Fistula (ISGPF) definition [48], while one article did not define the criteria used to assess for POPF [42]. Pooled analysis of the five high-quality studies did not demonstrate a relationship between intraoperative fluid management and POPF (OR 0.75, 95% CI 0.44–1.27, $p = 0.29$, $I^2 = 52\%$) (Fig. 2).

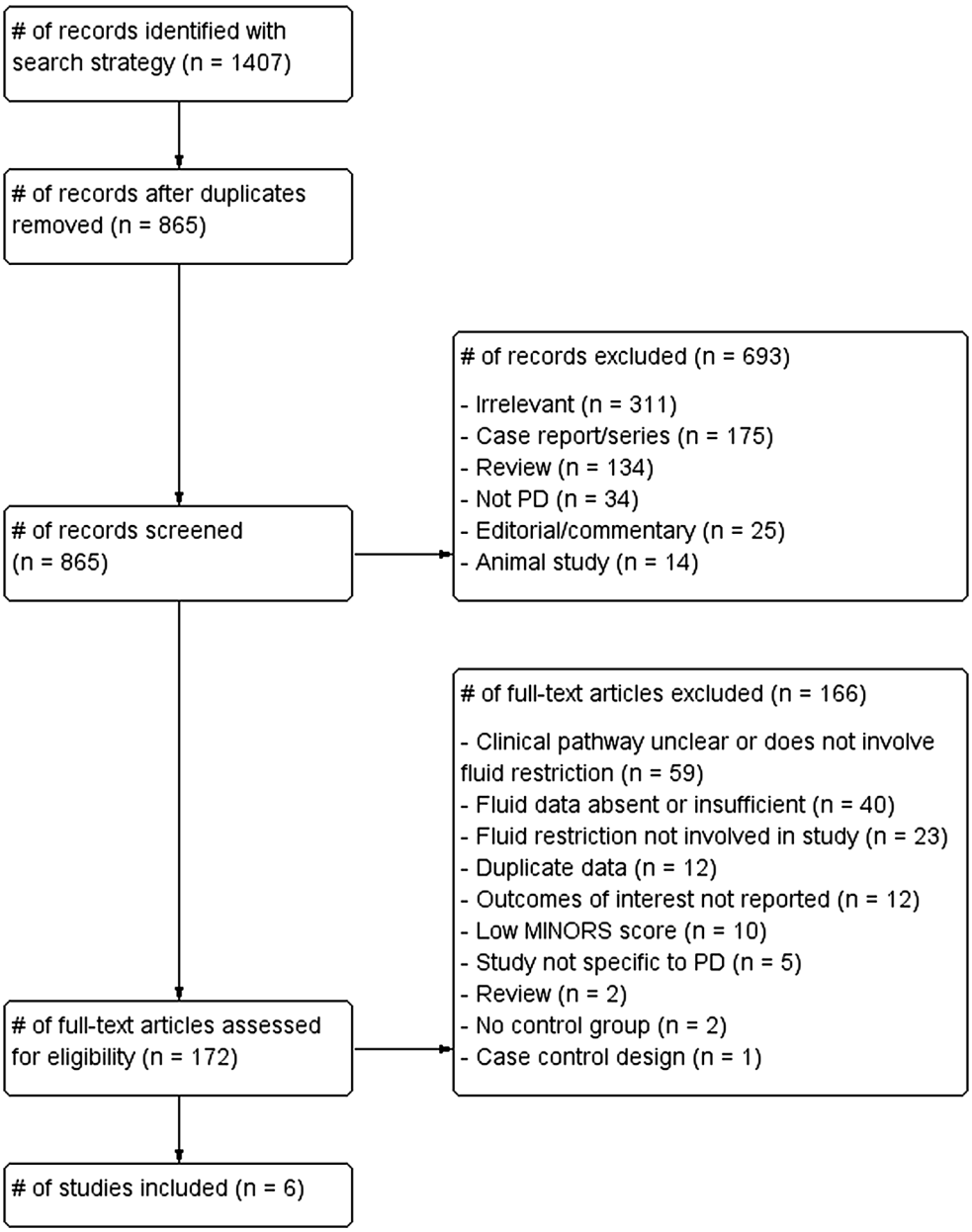


Fig. 1 Study selection flowchart

Delayed gastric emptying

Outcomes pertaining to DGE were reported in five studies [42–44, 46, 47], of which two used the International Study Group of Pancreatic Surgery (ISGPS) definition for DGE [49]. One article did not define their criteria for DGE [42], one article defined it as the need for nasogastric (NG) decompression beyond POD10 [47], and one article defined it as need for NG decompression or vomiting beyond POD10 [46]. Pooled analysis of five studies did not demonstrate a significant relationship between intraoperative fluid management and DGE (OR 0.72, 95% CI 0.47–1.11, $p = 0.13$, $I^2 = 0\%$) (Fig. 2).

Complication rate

Five studies reported overall complication rate, defined as the proportion of patients with at least one complication [42–44, 46, 47]. Studies reported a combination of POPF, DGE, hemorrhage/hematoma, infection, as well as cardiac, pulmonary, gastrointestional, and urogenital complications. One study [46] used the Dindo–Clavien classification system [50], one [42] used a severity classification system described by Grobmyer et al. [6], while the other papers did not use a standardized system. Pooled analysis of five studies did not demonstrate a significant association between complications and restrictive intraoperative fluid

Table 1 Characteristics of included studies and patient demographics

Study	Country	Years	Study design	Outcomes	*N*	Mean age (SD)	Gender (% male)	Indications for surgery	Type of crystalloid used
Van Samkar [44]	Netherlands	2006–2009	RCT	POPF, DGE, LOS, morbidity, mortality	66	NR	NR	Suspected pancreatic head or periampullary tumor	Ringer's Lactate
Braga [46]	Italy	2008–2012	Prospective database	POPF, DGE, LOS, morbidity, mortality, readmission	230	69.0 (2.2)	57.4%	NR	NR
Lavu [43]	US	2011–2013	RCT	POPF, DGE, LOS, morbidity, mortality, readmission	259	67.4 (11.0)	54.1%	Periampullary adenocarcinoma, cystic disease, neuroendocrine, pancreatitis, miscellaneous	Ringer's Lactate
Wang [47]	China	2005–2009	Retrospective	POPF, DGE, LOS, morbidity, mortality	147	53.5 (10.6)	72.8%	Benign or malignant pathology of the pancreas or periampullary region	Crystalloids (0.9% saline, 5% glucose, LR), colloids (HAES, albumin), blood
Fischer [42]	US	2005–2009	RCT	POPF, DGE, LOS, morbidity, mortality	130	64.5 (11.0)	53.1%	Pancreatic, biliary, ampullary, and duodenal cancer; IPMN, pancreatic endocrine neoplasm, others	Normosol (Hospira Inc, Lake Forest, Ill) – isotonic electrolyte solution similar in composition to Lactated Ringer's
Vermeulen [45]	Netherlands	2004–2005	RCT	LOS	14	62.5 (8.6)	78.6%	NR	Ringer's Lactate, mixture of 0.9% NaCl and 5% glucose

All patients were scheduled for PD, but some underwent palliative gastric bypass based on intraoperative findings

management (OR 0.79, 95% CI 0.60–1.04, $p = 0.09$, $I^2 = 0\%$) (Fig. 2).

Length of stay

Five studies reported LOS [42–44, 46, 47]. Pooled analysis of these studies did not demonstrate a relationship between intraoperative fluid management and LOS (MD 0.04, 95% CI −1.25 to 1.32, $p = 0.96$, $I^2 = 0$) (Fig. 2).

Mortality

Mortality was reported in five studies [42–44, 46, 47]. Hospital, 30-day, and 90-day mortality were each reported in two studies. Pooled analysis did not demonstrate relationships between intraoperative fluid management and in-hospital (OR 0.77, 95% CI 0.11–5.59, $p = 0.80$, $I^2 = 0\%$) (Appendix 2), 30-day (OR 0.81, 95% CI 0.23–2.87, $p = 0.74$, $I^2 = 0\%$) (Fig. 2), or 90-day mortality (OR 1.31, 95% CI 0.29–5.98, $p = 0.73$) (Appendix 2).

Readmission

Readmission rate was only reported in two studies [43, 46], and the follow-up period was variable; thus, pooled analysis was not performed. Both studies failed to find a significant difference between groups. Braga et al. reported a 12.2% 30-day readmission rate in the ERAS (restrictive) group, compared to 10.4% in the control (standard) group ($p = 0.835$) [46]. Similarly, Lavu et al. [43] reported a 12% readmission rate in the hypertonic saline (restrictive) group, compared to 10% in the lactated Ringers (standard)

Table 2 Definitions of "restrictive" and "standard" management

	Defining factor	Restrictive	Standard
van Samkar [44]	Randomization: intraoperative crystalloid infusion rate based on the literature	5 ml/kg/h	10 ml/kg/h
Braga [46]	Implementation of ERAS protocol (which included intraoperative fluid restriction, although details are not reported)	Post-implementation	Pre-implementation
Lavu [43]	Randomization: intra- and postoperative crystalloid infusion rate and type of fluid. Fluid protocols developed by a multidisciplinary group comprising of pancreatic surgeons and anesthesiologists based on institutional experience, standard intraoperative fluid paradigm, and the literature review	Intraoperative: 9 ml/kg/h LR, 1 ml/kg/h HYS Postoperative: 1 ml/kg/h HYS	Intraoperative: 15 ml/kg/h LR Postoperative: 2 ml/kg/h LR
Wang [47]	Intraoperative fluid infusion rate. Patients were retrospectively split into restrictive and standard groups using the mean infusion rate as the threshold	<8.2 ml/kg/h	≥8.2 ml/kg/h
Fischer [42]	Randomization: ANH or standard management	Standard management	ANH
Vermeulen [45]	Randomization: postoperative crystalloid infusion rate. 2.5 L/24 h was determined to be the standard fluid regime following an audit of university hospitals in the Netherlands and was thus set as the standard. 1.5L/24 h appears to have been chosen arbitrarily	1.5 L/24 h	2.5 L/24 h

ERAS enhance recovery after surgery, *LR* lactated Ringers, *HYS* 3% hypertonic saline, *ANH* acute normovolemic hemodilution

Table 3 Risk of bias within included studies (a) Cochrane Risk of Bias for randomized trials; (b) MINORS score for non-randomized studies

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete data outcome	Selective reporting	Other
(a)							
van Samkar [44]	L	NR	L	L	L	H	L
Lavu [43]	L	L	L	H	L	H	L
Fischer [42]	NR	NR	NR	NR	L	H	L
Vermeulen [45]	L	L	H	H	L	L	L
							MINORS score
(b)							
Braga [46]							18
Wang [47]							17

(a) H = high, L = low, ? = unclear

(b) Maximum score is 24 [38]. A score greater than or equal to 17 was considered high quality [39]

group. Follow-up time was not specified in this study, however.

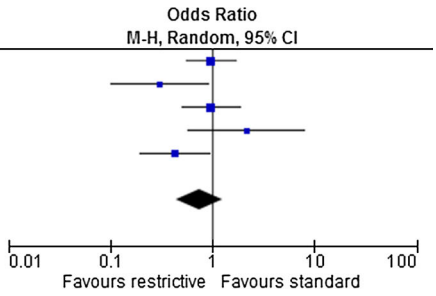
Postoperative fluid management

Two studies assessed the postoperative fluid management [43, 45]. Lavu et al. [43] conducted an RCT comparing hypertonic saline at a lower infusion rate and lactated ringers at a higher infusion rate. These fluid differences were maintained intraoperatively and postoperatively on POD0. On POD1, both groups were switched to dextrose 5% in 0.45% normal saline at the same infusion rate. The results of this study have been presented in the pooled analysis of intraoperative data. Vermeulen et al. [45] conducted an RCT exclusively comparing postoperative fluid restriction. Their study included 62 patients undergoing elective major abdominal surgery allocated to either a restricted (1.5 L/24 h) or standard (2.5 L/24 h) postoperative fluid regime. We contacted the authors to acquire raw data specific to PD patients ($n = 14$) and conducted statistical analysis on this subset of patients using the same test used by the authors (Mann–Whitney U). Average LOS

POPF

Study or Subgroup	Restrictive Events	Total	Standard Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Braga 2014	35	115	36	115	27.8%	0.96 [0.55, 1.68]
Fischer 2010	5	65	14	65	14.8%	0.30 [0.10, 0.90]
Lavu 2014	21	131	21	128	24.7%	0.97 [0.50, 1.88]
van Samkar 2015	8	34	4	32	11.5%	2.15 [0.58, 8.01]
Wang 2014	15	90	18	57	21.2%	0.43 [0.20, 0.95]
Total (95% CI)		**435**		**397**	**100.0%**	**0.75 [0.44, 1.27]**
Total events	84		93			

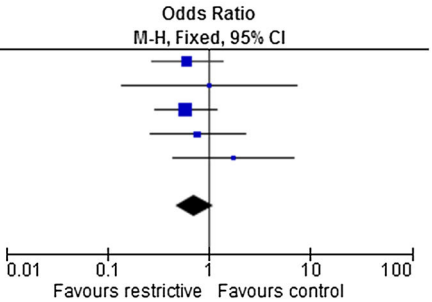
Heterogeneity: Tau² = 0.18; Chi² = 8.29, df = 4 (P = 0.08); I² = 52%
Test for overall effect: Z = 1.06 (P = 0.29)



DGE

Study or Subgroup	Standard Events	Total	Restrictive Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Braga 2014	11	115	17	115	31.5%	0.61 [0.27, 1.37]
Fischer 2010	2	65	2	65	4.0%	1.00 [0.14, 7.32]
Lavu 2014	15	131	23	128	42.2%	0.59 [0.29, 1.19]
van Samkar 2015	13	30	12	24	15.5%	0.76 [0.26, 2.25]
Wang 2014	8	90	3	57	6.9%	1.76 [0.45, 6.92]
Total (95% CI)		**431**		**389**	**100.0%**	**0.72 [0.47, 1.11]**
Total events	49		57			

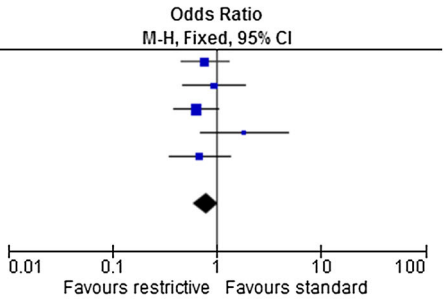
Heterogeneity: Chi² = 2.21, df = 4 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)



Complications

Study or Subgroup	Restrictive Events	Total	Standard Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Braga 2014	69	115	76	115	26.7%	0.77 [0.45, 1.32]
Fischer 2010	31	65	32	65	14.7%	0.94 [0.47, 1.87]
Lavu 2014	56	131	69	128	35.1%	0.64 [0.39, 1.04]
van Samkar 2015	21	34	15	32	5.2%	1.83 [0.69, 4.88]
Wang 2014	39	90	30	57	18.3%	0.69 [0.35, 1.34]
Total (95% CI)		**435**		**397**	**100.0%**	**0.79 [0.60, 1.04]**
Total events	216		222			

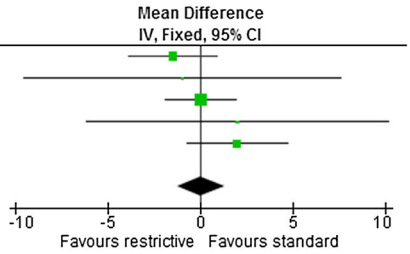
Heterogeneity: Chi² = 3.97, df = 4 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.69 (P = 0.09)



LOS

Study or Subgroup	Restrictive Mean	SD	Total	Standard Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Braga 2014	14.6	9.8	115	16.1	8.9	115	28.3%	-1.50 [-3.92, 0.92]
Fischer 2010	7	14.75	65	8	32	65	2.3%	-1.00 [-9.57, 7.57]
Lavu 2014	7	9.33	131	7	6.167	128	44.8%	0.00 [-1.92, 1.92]
van Samkar 2015	12	8.598	34	10	22.189	32	2.5%	2.00 [-6.21, 10.21]
Wang 2014	21.53	9.24	90	19.57	7.54	57	22.2%	1.96 [-0.77, 4.69]
Total (95% CI)			**435**			**397**	**100.0%**	**0.04 [-1.25, 1.32]**

Heterogeneity: Chi² = 3.73, df = 4 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.96)



30-Day Mortality

Study or Subgroup	Restrictive Events	Total	Standard Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Braga 2014	4	115	4	115	71.9%	1.00 [0.24, 4.10]
Lavu 2014	0	131	1	128	28.1%	0.32 [0.01, 8.01]
Total (95% CI)		**246**		**243**	**100.0%**	**0.81 [0.23, 2.87]**
Total events	4		5			

Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

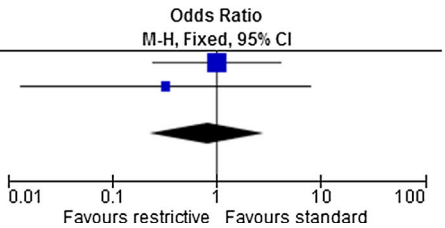


Fig. 2 Forest plots for meta-analysis of pancreatic fistula, delayed gastric emptying, complications, length of stay, and 30-day mortality

for patients in the restricted group was 20.8 days (range 11–72 days), compared to 9.8 days (range 8–20 days) in the standard group ($p = 0.042$).

Discussion

Previous reviews of perioperative fluid management have focused on colorectal surgery [31] or intraabdominal surgery in general [32, 33]. In this paper, we reviewed the literature on perioperative fluid management in PD and pooled data from RCTs and high-quality observational studies. There was no relationship between intraoperative fluid management and any of outcomes of interest: POPF, DGE, complications, LOS, mortality, and hospital readmission. Only one study exclusively compared postoperative fluid management and found longer LOS associated with patients in the restricted postoperative fluid group [45]. However, given the small sample size of patients undergoing PD in this study ($n = 14$), the results must be interpreted with caution.

Fluid replacement is simple in theory: replace what is lost and avoid fluid overload [51]. However, the difficulty lies in accurately determining the volume of fluids to be replaced. With the advent of noninvasive physiologic monitoring tools, an increasing number of trials are exploring goal-direct fluid therapy (GDFT), which focuses on using physiologic proxies of tissue perfusion to guide fluid administration [22, 52, 53]. Although many physiologic directed measurements, such as systolic pressure variation, stroke volume variation, and central venous pressure, have been studied, there remains no consensus on the most appropriate target [53]. Furthermore, high-quality evidence is lacking [54] and a recent systematic review did not find convincing evidence that intraoperative GDFT significantly improved short-term outcomes over conventional fluid management in patients undergoing major abdominal surgery, especially if patients were managed on an enhanced recovery pathway [55].

Restrictive fluid management remains controversial in general surgery. Most published guidelines for perioperative fluid management advocate for fluid restriction, although most of these are not specific to PD. A consensus statement from the enhanced recovery partnership in England recommended avoiding excess crystalloids, limiting maintenance fluids intraoperatively, and avoiding postoperative intravenous fluids if possible [52]. The International Fluid Optimization Group recommends restrictive maintenance fluids for major and lengthy procedures (>6 h), but suggests a possible benefit of higher fluid administration rates for smaller outpatient procedures [53]. The ERAS society's guidelines for PD call for "near zero fluid balance," but this recommendation is based primarily on evidence from colorectal surgery [56].

A meta-analysis of RCTs found decreased overall morbidity in patients managed with a restrictive fluid protocol for colorectal surgery [31]. A subsequent meta-analysis of RCTs evaluating fluid restriction in major abdominal surgery failed to find any effect, even though 5 of 7 studies included in the meta-analysis featured primarily or exclusively patients undergoing colorectal surgery [32]. Varadhan and Lobo suggested that fluid balance is more important than fluid administration by demonstrating superior outcomes in patients managed in a state of fluid "balance" rather than "imbalance" following major elective open abdominal surgery [33]. Given that PD is a lengthy procedure with extensive retroperitoneal dissection, it is plausible that patients experience greater insensible fluid losses than colorectal resection. As such patients may be closer to a zero fluid balance at the same rate of fluid administration. This may partially account for the lack of benefit with restrictive fluid management in these patients.

This paper reviewed the best available evidence in restrictive fluid management in PD by pooling data from RCTs and high-quality observational studies, but major limitations remain. The variability in defining "restrictive" and "standard" fluid management between studies is perhaps the most significant limitation. In part, the lack of evidence-based recommendations for perioperative fluid management contributes to this inconsistency [25, 51]. This variation is highlighted in Table 2. In many retrospective studies, authors simply stratified patients into groups using the median fluid volume as a cutoff. The RCTs were also heterogeneous. Among the three RCTs, one restricted intraoperative fluids, one restricted both intra- and postoperative fluids, and the other was not originally designed to compare fluid restriction, but rather to evaluate acute normovolemic hemodilution [42]. Furthermore, included studies were not consistent in the type of crystalloid used. This is further complicated with one study using colloids as a strategy to restrict the total fluid administration [43]. Despite the heterogeneity in study design, there was minimal statistical heterogeneity in the results ($I^2 = 0\%$ for all outcomes except POPF). In addition, means and standard deviations were estimated for studies that reported median and range for LOS [40]. While this estimation method receives widespread use and acceptance, it remains an estimate rather than a precise value. Lastly, only one study exclusively assessed the impact of postoperative fluid restriction [45]; thus, it is difficult to draw conclusions about the utility of postoperative fluid restriction. Additionally, this trial was terminated prematurely after failing to reach their target number of patients within the planned timeframe. Furthermore,

study protocol was frequently violated due to postoperative hypotension, oliguria, or infusion pump problems that lead to additional fluid boluses being given or incorrect volumes infused.

Conclusion

Pooled analysis of the best available evidence showed that restrictive intraoperative fluid management did not have an effect on postoperative outcomes in patients undergoing PD. Pooled studies were heterogeneous in their study design, the most notable issue being the variability in defining "restrictive" and "standard" fluid management. Thus, these results should be interpreted with caution. To date, there are too few studies specific to PD assessing postoperative fluid restriction to draw a conclusion with regards to its efficacy.

Appendix 1: Search strategy

Database: Embase Classic + Embase <1947 to 2017 April 11>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 pancreas resection/(18092)
2 pancreaticoduodenectomy/(19623)
3 (whipple$ adj5 (pancrea$ or surg$ or resect$ or procedure$ or operation$)).tw. (4368)
4 (Pancreatectom$ or pancreatoduodenectom$ or Pancreaticoduodenectom$ or duodenopancreatectom$ or pancreat$ duodenectom$).tw. (34610)
5 ((duodenopancrea$ or pancrea$) adj2 resect$).tw. (14789)
6 ((duodenopancrea$ or pancrea$) adj2 (surg* or resect$)).tw. (22187)
7 or/1-6 (60116)
8 fluid therapy/or fluid resuscitation/(40831)
9 rehydration/(21709)
10 crystalloid/(6023)
11 colloid/(39788)
12 isotonic solution/(12623)
13 (crystalloid* or colloid*).tw. (105122)
14 (fluid adj3 (balance or intervention or management or volume or therapy or replacement or restriction or resuscitation)).tw. (59280)
15 (volume adj3 (balance or intervention or management or therapy or replacement or restriction or resuscitation)).tw. (11794)
16 hetastarch/or Ringer lactate solution/or sodium chloride/(228503)
17 (ringer* adj2 lactate*).tw. (8908)
18 hypertonic solution/(6263)
19 d5w.tw. (620)
20 dextrose.tw. (21245)
21 (saline or sodium chloride).tw. (374747)
22 or/8-21 (716901)
23 7 and 22 (803)
24 (enhanced recovery or eras).tw. (8409)
25 clinical pathway/(11909)
26 (caremap* or care map*).tw. (500)
27 (care adj (plan* or pathway*)).tw. (28718)
28 ((critical or clinical) adj pathway*).tw. (8531)
29 (early recovery or fast track* or fasttrack*).tw. (11746)
30 early discharge.tw. (5089)
31 or/24-30 (67709)
32 7 and 31 (293)
33 23 or 32 (1074)
34 (exp animal/or non-human/) not exp human/(10231631)
35 33 not 34 (907)
36 35 use emczd (639)
37 Pancreatectomy/(28609)
38 Pancreaticoduodenectomy/(19623)
39 (whipple$ adj5 (pancrea$ or surg$ or resect$ or procedure$ or operation$)).tw. (4368)
40 (Pancreatectom$ or pancreatoduodenectom$ or Pancreaticoduodenectom$ or duodenopancreatectom$ or pancreat$ duodenectom$).tw. (34610)
41 ((duodenopancrea$ or pancrea$) adj2 (surg* or resect$)).tw. (22187)
42 or/37-41 (64033)
43 Fluid Therapy/(33370)
44 Rehydration Solutions/(3776)
45 Isotonic Solutions/(12623)
46 exp Colloids/(126940)
47 (fluid adj3 (balance or intervention or management or volume or therapy or replacement or restriction or resuscitation)).tw. (59280)
48 (volume adj3 (balance or intervention or management or therapy or replacement or restriction or resuscitation)).tw. (11794)
49 (colloid* or crystalloid*).tw. (105122)
50 (ringer* adj2 lactate*).tw. (8908)
51 Sodium Chloride/(216552)
52 exp Hypertonic Solutions/(17443)
53 Hypotonic Solutions/(5403)
54 d5w.tw. (620)
55 dextrose.tw. (21245)
56 (saline or sodium chloride).tw. (374747)
57 or/43-56 (795825)
58 42 and 57 (816)
59 (early recovery or eras).tw. (10579)
60 Critical Pathways/(11909)
61 (caremap* or care map*).tw. (500)
62 (care adj (plan* or pathway*)).tw. (28718)

63	((critical or clinical) adj pathway*).tw. (8531)
64	(enhanced recovery or fast track* or fasttrack*).tw. (10125)
65	early discharge.tw. (5089)
66	or/59-65 (67709)
67	42 and 66 (304)
68	58 or 67 (1097)
69	animals/not humans/(5296415)
70	68 not 69 (1003)
71	70 use prmz (307)
72	36 or 71 (946)
73	remove duplicates from 72 (694)
74	**73 use prmz (305)Medline**
75	**73 use emczd (389)Embase**

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((((((((((((((((“volume replacement”) OR “volume balance”) OR “volume intervention”) OR “volume management”) OR “volume therapy”) OR “volume restriction”) OR “volume resuscitation”))) OR (((((((((“fluid balance”) OR “fluid intervention”) OR “fluid management”) OR “fluid therapy”) OR “fluid volume”) OR “fluid replacement”) OR “fluid restriction”) OR “fluid resuscitation”) OR fluid[Title])) OR ((ringers[Title/Abstract] AND lactate[Title/Abstract]))) OR ((ringers[Title/Abstract] AND lactated[Title/Abstract]))) OR (“enhanced recovery” or fast track or fasttrack or early discharge or “critical path*” or “clinical path*” or “care plan” or “care map*”)) OR ((((((saline) OR sodium chloride))) OR dextrose[Title/Abstract]))) OR ((colloid*[Title/Abstract]) OR crystalloid*[Title/Abstract]))) AND ((((((((((pancreaticoduodenectomy[Title/Abstract]) OR pancreaticoduodenectomy[Other Term]) OR pancreas resection[Title/Abstract]) OR pancreas resection[Other Term]) OR pancreas surgery[Title/Abstract]) OR pancreas surgery[Other Term]) OR whipple[Title/Abstract]) OR whipple[Other Term]) OR Pancreatectomy[Title/Abstract]) OR Pancreatectomy[Other Term]))) AND (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]) – 8 references

Cochrane

Search Name: Martel-Guillaume_Pancreaticoduodenectomy-Fluids_2016-01-12

Date Run: January 12, 2016, 18:35:22.802

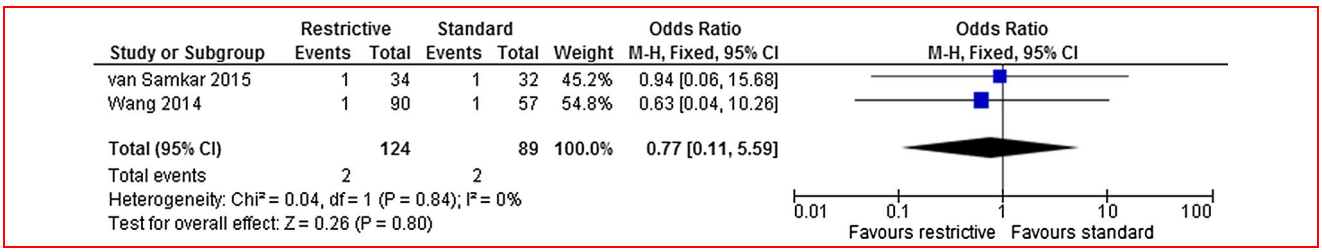
Description:

ID	Search	Hits
#1	MeSH descriptor: [Pancreatectomy] explode all trees	180
#2	MeSH descriptor: [Pancreaticoduodenectomy] explode all trees	235
#3	whipple* near/5 (pancrea* or surg* or resect* or procedure* or operation*):ti,ab,kw (Word variations have been searched)	78
#4	Pancreatectom* or pancreatoduodenectom* or Pancreaticoduodenectom* or duodenopancreatectom* or pancreat* duodenectom*:ti,ab,kw (Word variations have been searched)	608
#5	(duodenopancrea* or pancrea*) near/2 (surg* or resect*):ti,ab,kw (Word variations have been searched)	722
#6	#1 or #2 or #3 or #4 or #5	1048
#7	MeSH descriptor: [Fluid Therapy] explode all trees	1289
#8	MeSH descriptor: [Rehydration Solutions] explode all trees	264
#9	MeSH descriptor: [Isotonic Solutions] explode all trees	701
#10	MeSH descriptor: [Colloids] explode all trees	5708
#11	fluid near/3 (balance or intervention or management or volume or therapy or replacement or restriction or resuscitation):ti,ab,kw (Word variations have been searched)	3861
#12	volume near/3 (balance or intervention or management or therapy or replacement or restriction or resuscitation):ti,ab,kw (Word variations have been searched)	1145
#13	colloid* or crystalloid*:ti,ab,kw (Word variations have been searched)	2211
#14	ringer* near/2 lactate*:ti,ab,kw (Word variations have been searched)	740
#15	MeSH descriptor: [Sodium Chloride] this term only	1906
#16	MeSH descriptor: [Hypertonic Solutions] explode all trees	595
#17	MeSH descriptor: [Hypotonic Solutions] explode all trees	63
#18	d5w:ti,ab,kw (Word variations have been searched)	49
#19	“dextrose”:ti,ab,kw (Word variations have been searched)	1134
#20	saline or sodium chloride:ti,ab,kw (Word variations have been searched)	20761
#21	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20	32766
#22	#6 and #21	46
#23	(early recovery or eras):ti,ab,kw (Word variations have been searched)	5535
#24	MeSH descriptor: [Critical Pathways] explode all trees	278
#25	(caremap* or care map*):ti,ab,kw (Word variations have been searched)	669
#26	care near (plan* or pathway*):ti,ab,kw (Word variations have been searched)	2295

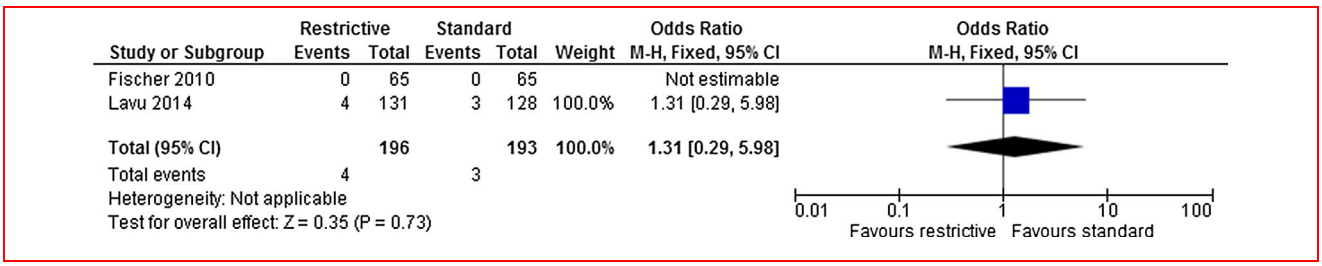
ID	Search	Hits
#27	(critical or clinical) near pathway*:ti,ab,kw (Word variations have been searched)	645
#28	(enhanced recovery or fast track* or fasttrack*):ti,ab,kw (Word variations have been searched)	2559
#29	early discharge:ti,ab,kw (Word variations have been searched)	3035
#30	#23 or #24 or #25 or #26 or #27 or #28 or #29	13343
#31	#6 and #30	36
#32	#22 or #31	68 Clinical Trials

Appendix 2: Forest plots for in-hospital and 90-day mortality

In-hospital mortality



90-day mortality



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