Preoperative Stenting for Benign and Malignant Periampullary Diseases

Unnecessary if Not Harmful

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KEYWORDS

- Preoperative stenting • Obstructive jaundice • Periampullary cancer
- Preoperative biliary drainage

KEY POINTS

- Preoperative biliary drainage (PBD) is often performed in patients with jaundice with the presumption that it will decrease the risk of postoperative complications.
- PBD carries its own risk of complications and, therefore, has been controversial.
- Multiple randomized controlled trials and metaanalyses have shown that PBD has significantly increased overall complications compared with surgery alone.
- The routine application of PBD should be avoided except in a subset of clinical situations.

INTRODUCTION

Although many patients are asymptomatic, among the leading symptoms at initial presentation of patients with a periampullary tumor is pruritus from icterus or obstructive jaundice. It is established that surgery in patients with jaundice can lead to coagulopathy, infection, renal dysfunction, and an increased risk of postoperative complications and worse outcomes.[1,2] Hyperbilirubinemia has been identified as a risk factor for poor outcomes in numerous studies.[3–5] It was believed that by reversing this pathophysiologic disturbance, preoperative biliary drainage (PBD) would lead to improved outcomes in patients with jaundice. Dr AO Whipple and colleagues[6] suggested that a 2-staged surgical approach, by use of a bypass to reduce preoperative hyperbilirubinemia, would improve hepatic function in patients with obstructive jaundice, whereas Brunschwig[7] at the authors' institution reported a 1-stage procedure in 1937. Currently, PBD is mostly achieved by placement of a common bile duct stent during diagnostic endoscopic

This study was supported in part by NIH/NCI P30 CA008748 (Cancer Center Support Grant).
Disclosure Statement: The authors have nothing to disclose.
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Surg Clin N Am 98 (2018) 37–47
https://doi.org/10.1016/j.suc.2017.09.005
surgical.theclinics.com

retrograde cholangiopancreatography or, alternatively, by percutaneous transhepatic drainage before surgical intervention.[8,9] Although initial studies showed that PBD may reduce postoperative mortality rates in jaundiced patients, more recent publications have challenged such results and presumed advantages of PBD.[10,11] This article reviews the most relevant data regarding the use of PBD in patients with benign and malignant periampullary tumors, and presents the authors' current practice and recommendations.

THE PROBLEM: INCREASED INFECTIOUS COMPLICATIONS WITH PREOPERATIVE BILIARY DRAINAGE

PBD before pancreaticoduodenectomy leads to colonization of sterile bile and consequently increases risk of infections, including surgical site infection, cholangitis, and sepsis. Numerous studies have shown that subjects undergoing PBD have higher rates of positive intraoperative bile cultures and carry higher infectious-related morbidity and mortality. In an early study from the authors' institution, Povoski and colleagues[12] reviewed 161 subjects who underwent pancreaticoduodenectomy with available intraoperative bile cultures and showed positive bile cultures in 58% of subjects and similar organism profiles of intraoperative bile cultures and associated blood cultures. On multivariate analysis, the investigators showed that PBD was associated with increased risk of postoperative infectious complications, including wound infections, intraabdominal abscess formation, and death. Together, their results suggested that PBD should be avoided due its associated complication rates.

PREOPERATIVE BILIARY DRAINAGE VERSUS EARLY SURGERY: REVIEW OF CURRENT DATA

Randomized Controlled Trials

Six randomized controlled trials (RCTs) failed to show any significant clinical benefit from routine stenting and demonstrated increased postoperative complications and poor outcome. The presumed benefits of PBD are largely theoretic.

The best designed multicenter RCT, from the Netherlands, examined 202 subjects with periampullary tumors and obstructive jaundice (bilirubin level 2.3–14.6 mg/dL) who were randomized to PBD for 4 to 6 weeks versus surgery alone within 1 week of study enrollment.[13] The primary examined outcome was the rate of severe complications during the treatment and within 120 days of randomization. A severe complication was defined as any complication related to endoscopic biliary drainage or the surgical procedure leading to additional invasive interventions and subsequent increased length of stay, readmission for disease related morbidity, or mortality. Secondary endpoints evaluated were number of invasive procedures, costs, length of hospital stay, and quality of life. PBD was successful in 94% of the subjects with a complication rate of 46%. The trial showed a lower rate of serious complications in the early surgery group compared with PBD (39% vs 74%; risk ratio [RR] = 0.54, 95% CI 0.41–0.71, $P<.001$), with equivalent postoperative surgical complication rates, mortality, and hospital stay. Based on the increased complication and morbidity, the investigators concluded that routine use of PBD in patients with obstructive jaundice was not recommended.

Similarly, other RCTs have shown that PBD is associated with equivalent or higher complication rates.[14–17] Drainage-related complication rates, hospital stay, overall morbidity, and mortality reported in these individual studies are summarized in **Table 1**.

Retrospective Studies, Metaanalysis, and Reviews

A series of retrospective studies, summarized in **Table 2**, have been published on this topic. Most of these show that PBD is associated with higher infectious

Table 1
Randomized controlled trials of preoperative biliary drainage versus direct surgery for obstructive jaundice

Study, Year	Total Number of Subjects	Treatment Group	Number of Subjects	Drainage Route	Drainage-Related Complication Rate (%)	Hospital Stay (d)	Morbidity (%)	Mortality Number (%)
Hatfield et al,[14] 1982	57	PBD	28	PTBD	>50	NA	14	4 (14)
		DS	29				14	4 (14)
Lai et al,[15] 1994	87	PBD	43	Endoscopic	28	NA	37	6 (14)
		DS	44				41	6 (14)
McPherson et al,[16] 1984	65	PBD	34	PTBD	>50	40	39	11 (31)
		DS	31			23	41	6 (19)
Pitt et al,[17] 1985	75	PBD	37	PTBD	27	31	57	3 (8)
		DS	38			23	53	2 (5)
Van der Gaag et al,[13] 2010	202	PBD	102	Endoscopic	46	15	47[a]	15 (15)
		DS	96			13	37	12 (13)

Abbreviations: DS, direct surgery; NA, not available; PTBD, percutaneous transhepatic biliary drainage.
[a] Statistically significant difference with $P<.05$.

Table 2
Retrospective series of preoperative biliary stent versus no stent for obstructive jaundice

Reference, Year	N	Group	Infectious Complications (%)	Wound Infections (%)	Intraabdominal Abscess (%)	Pancreatic Leak or Fistula (%)	Morbidity (%)	Mortality (%)
Povoski et al,[12] 1999	126	Stented	41[a]	NA	19[a]	NA	55[a]	8[a]
	114	Unstented	25	NA	8	NA	39	3
Sohn et al,[18] 2000	408	Stented	32	10	4	10	35	2
	159	Unstented	22	4	6	4	30	3
Pisters et al,[19] 2001	172	Stented	37	13[a]	39	0	88	1
	93	Unstented	31	4	37	0	86	1
Martignoni et al,[20] 2001	99	Stented	25	5	0	1	50	2
	158	Unstented	22	6	3	3	45	3
Srivastava et al,[21] 2001	54	Stented	52[a]	43[a]	28[a]	20[a]	48	15
	67	Unstented	29	24	15	5	46	12
Sewnath et al,[22] 2002	232	Stented	37	7	16	14	50	1
	58	Unstented	31	9	16	7	55	0
Mezhir et al,[23] 2009	94	Stented	32[a]	20[a]	12[a]	4	51	0
	94	Unstented	13	7	3	6	41	5
Coates et al,[24] 2009	56	Stented	18	5	7	7	37	4
	34	Unstented	21	9	12	12	47	15

[a] Statistically significant difference between stented and unstented group with $P<.05$.

complications,[12,21,23] increased wound infections and intraabdominal abscesses,[12,21,23] pancreatic fistula rate,[21] and higher overall morbidity and mortality rates[12]

A metaanalysis by Sewnath and colleagues[22] showed that PBD carried no benefit and thus was not recommended to be performed routinely for malignant obstructive jaundice. Similarly, a Cochrane review published in 2008 demonstrated no clear evidence for routine drainage in this patient population.[25] Most recently, Fang and colleagues[26] reanalyzed and updated the previous metaanalysis to include the newest trial by van der Gaag and colleague.[13] This study of 520 subjects reviewed 6 randomized studies evaluating the safety and effectiveness of PBD (n = 265) versus no drainage with early surgery (n = 255). Two out of the 6 randomized trials used an endoscopic approach and 4 used a transhepatic biliary approach with a wide range of duration of drainage in 4 trials (reported mean of 7–43 days and 4–6 weeks[13]). For outcomes, they assessed rate of serious morbidity and mortality, length of hospital stay, cost, and quality of life.

The data extraction was performed by 2 independent reviewers who identified higher overall serious morbidity (grade III or IV, Clavien-Dindo classification) in the PBD group compared with early surgery (RR = 1.66; 95% CI 1.28–2.16, P<.001) without a significant difference in mortality (RR = 1.12; 95% CI 0.73–1.71, P = .60). Additionally, the investigators showed no significant difference in length of hospital stay between the 2 groups (mean difference of 4.48 days; 95% CI 1.28–11.28, P = .12). Quality of life and cost data were not reported in any of the trials to draw any objective conclusions about those outcomes. Based on these results, the investigators concluded that combination of PBD followed by surgery increased the rate of serious complications compared with that of surgery alone, without significant clinical advantages. Outcomes for serious complications and mortality and published forest plots are presented in **Figs. 1** and **2**, respectively.

EFFECTS ON PREOPERATIVE BILIARY DRAINAGE ON SURVIVAL

Whether PBD and the associated delay in surgery in patients with malignant pancreatic head tumors affects survival was evaluated in a multicenter trial by Eshuis and colleagues.[27] Subjects with a bilirubin of 2 to 14 mg/dL were randomized into drainage group (PBD) for 4 to 6 weeks or to proceed with early surgery (ES; <1 week). The

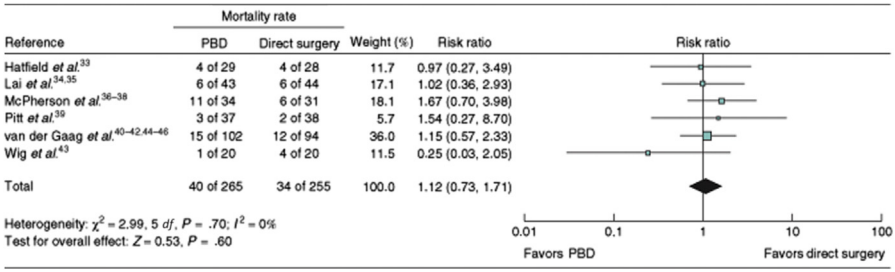

Fig. 1. Mortality rates and forest plot of randomized trials reported on PBD before surgery compared with direct surgery. A Mantel–Haenszel fixed-effect model was used for metaanalysis. RRs are shown with 95% CI. *df*, degrees of freedom. (*From* Fang Y, Gurusamy KS, Wang Q, et al. Meta-analysis of randomized clinical trials on safety and efficacy of biliary drainage before surgery for obstructive jaundice. Br J Surg 2013;100(12):1593; with permission.)

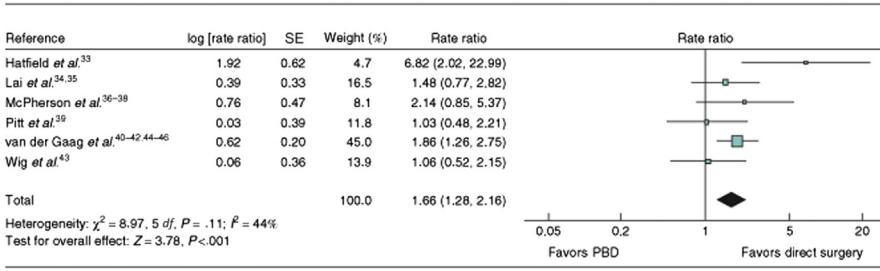

Fig. 2. Adverse events in trials that used PBD before surgery and those that did not (direct surgery). Data are shown in a logarithmic scale. An inverse-variance fixed-effect model was used for metaanalysis. Rate ratios are shown with 95% CI. (*From* Fang Y, Gurusamy KS, Wang Q, et al. Meta-analysis of randomized clinical trials on safety and efficacy of biliary drainage before surgery for obstructive jaundice. Br J Surg 2013;100(12):1593; with permission.)

investigators found that PBD and the associated delay in surgery did not affect overall survival compared with early surgery. The median survival times were comparable at 12.2 and 12.7 months in the ES and PBD group, respectively (**Fig. 3**). There was no difference in complete resection (R0) rates (73% in the ES group vs 62% in the PBD group). Univariate and multivariate analysis of predictive factors affecting overall survival of subjects who underwent surgery is shown in **Table 3**.

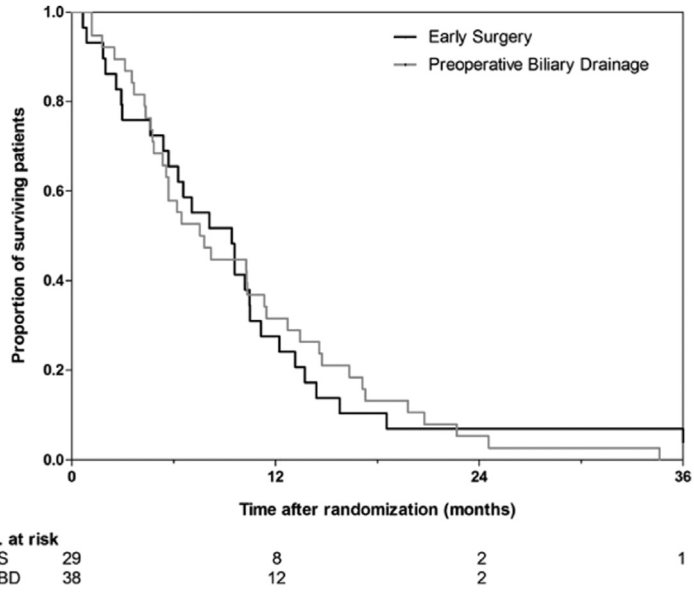

Fig. 3. Overall survival of patients with malignant pancreatic head tumors who were randomized to early surgery (ES) or PBD and underwent subsequent resection. (*From* Eshuis WJ, van der Gaag NA, Rauws EA, et al. Therapeutic delay and survival after surgery for cancer of the pancreatic head with or without preoperative biliary drainage. Ann Surg 2010;252(5):1593; with permission.)

Table 3
Univariate and multivariate analysis of predictive factors for overall survival in 180 subjects who underwent surgery for a malignant pancreatic head mass

	Univariable, HR (95% CI)	Multivariable, HR (95%)
Time from randomization to surgery 1-wk increment	0.98 (0.92–1.05)	0.91 (0.84–0.99)[a]
Age, 1-y increment[b]	1.00 (0.98–1.02)	1.00 (0.98–1.01)
Female sex	1.06 (0.76–1.48)	1.26 (0.87–1.80)
Bilirubin at randomization (quartiles), 1 quartile increment	1.17 (1.01–1.35)[a]	1.22 (1.04–1.43)[a]
Underwent PBD	0.90 (0.65–1.24)	NA
Resection of tumor	0.32 (0.23–0.46)[c]	0.28 (0.20–0.41)[c]
Blood transfusion intraoperatively	1.10 (0.71–1.71)	1.25 (0.79–1.98)
Complications related to PBD and/or surgery	1.09 (0.79–1.51)	1.45 (1.01–2.09)[a]

Abbreviation: HR, hazard ratio.
[a] Significant at $P<.05$ level.
[b] At the time of surgery.
[c] Significant at $P<.01$ level.
From Eshuis WJ, van der Gaag NA, Rauws EA, et al. Therapeutic delay and survival after surgery for cancer of the pancreatic head with or without preoperative biliary drainage. Ann Surg 2010;252(5):845; with permission.

PLASTIC VERSUS METAL STENTS

In patients with unresectable pancreatic head tumors, metal stents are superior and preferred compared with plastic stents, whether the same is true for patients with resectable tumors when early surgery is not feasible remains an area of controversy. An attempt to answer this question was made by Crippa and colleagues[28] in a meta-analysis of 5 studies, including 1 prospective trial[29] and 4 retrospective studies,[30–33] with a total of 704 subjects (**Table 4**). The investigators evaluated the rate of endoscopic reintervention (stent failure) and overall complications as primary and secondary outcomes, respectively. They demonstrated that the rate of PBD stent failure was significantly lower in the metal stent group (3.4%) than in the plastic stent group (14.8%) (odds ratio [OR] = 0.15, 95% CI 0.05–0.46, $P = .0009$). Overall complications were lower in the metal stent group compared with the group of subjects with plastic stents (OR = 0.64, 95% CI 0.37–1.10, $P = .11$). The investigators concluded that metal stents are more effective than plastic stents and should be preferred when early surgery without PBD is not feasible. This study has several limitations, including the retrospective nature of most of the studies and lack of information regarding the specific stent type reported in most studies.

COSTS OF PREOPERATIVE BILIARY DRAINAGE

Given the increased complication rate and morbidity associated with PBD, a British group evaluated the economic implications of PBD versus direct surgery for subjects with obstructive jaundice.[34] In their model, the investigators estimated the mean costs and quality-adjusted life years per patient in the UK National Health Service over 6 months and demonstrated that PBD was more costly than surgery alone (mean cost per patient $15,616 compared with $11,914). They reported fewer quality-adjusted life years per patient in the PBD group (mean 0.337 vs 0.343). Based on their

Table 4
Summary of studies comparing plastic versus metal stents and reported rates of stent failure, overall complications, and postoperative mortality rates

Reference, Year	Study Design	Total Number of Subjects	Type of Stent (N)	Rate of Stent Failure (%)	Overall Complications Rate Related to Drainage Before Surgery (%)	Overall Pancreatic Anastomotic Leak (%)	Overall Postoperative Mortality (%)
Tol et al,[29] 2016	Prospective	151	Plastic (102)	30	46	8	15
	Multicenter	—	Metal (49)	4	24	2	6
Haapamäki et al,[30] 2014	Retrospective	191	Plastic (163)	7	3	15	0
	—	—	Metal (28)	3	4	7	0
Cavell et al,[31] 2013	Retrospective	220	Plastic (149)	NA	NA	13	0
	—	—	Metal (71)	NA	NA	7	0
Adams et al,[32] 2012	Retrospective	113	Plastic (70)	NA	21	NA	NA
	—	—	Metal (43)	NA	3	NA	NA
Decker et al,[33] 2011	Retrospective	29	Plastic (18)	39	NA	0	NA
	—	—	Metal (11)	0	NA	0	NA

statistical model, they calculated a cost savings of more than $3600 per patient when PBD was avoided. These results present evidence to avoid interventions that are not clinically necessary.

INDICATIONS FOR PREOPERATIVE STENTING FOR SELECTED CLINICAL SITUATION

There are several clinical circumstances in which the authors think that PBD could be beneficial. First, one should consider PBD in patients with debilitating pruritus or in cases when further extended workup is needed or a surgical intervention cannot be scheduled in a timely fashion for logistical reasons. Another group of patients in whom PBD is recommended is those who present with signs of systemic infections, such as cholangitis, and require emergent decompression. PBD is typically recommended in cases with secondary systemic organ dysfunction, most importantly compromised renal function or anticipated major vascular reconstruction, to avoid increased risks of vascular thrombosis and liver ischemia. PBD is also indicated in patients who are scheduled to receive neoadjuvant systemic therapy before surgical intervention. A metal stent should be used in these situations due to better stent patency and lower reintervention and complication rates. The level of bilirubin that should stimulate a discussion about whether to stent is unknown; because 14 mg/dL has been used as the upper limit of bilirubin level in RCTs, values above that level could be used to consider stenting.

SUMMARY AND AUTHORS' RECOMMENDATIONS

The authors do not recommend routine PBD in asymptomatic jaundiced patients with benign or malignant periampullary tumors before resection. We prefer selective PBD for patients with long-standing jaundice or cholangitis, renal impairment, severe malnutrition, neoadjuvant chemotherapy, debilitating pruritus affecting quality of life, or any special circumstance that delays a surgical procedure. We prefer the endoscopic approach for biliary drainage for periampullary tumors. Percutaneous transhepatic biliary drainage should be undertaken only in cases of failure of endoscopic approaches.

In the selected cases previously outlined, we recommend admitting the patient the night before surgery for hydration to prevent postoperative renal insufficiency. Despite the lack of benefit proven by several level 1 data, most patients are evaluated and stented before surgical evaluation. The authors stress the need for comprehensive surgical evaluation before a decision concerning to invasive biliary drainage.

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