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Preoperative Biliary Drainage in Patients with Obstructive Jaundice: History and Current Status

N. A. van der Gaag · J. J. Kloek · S. M. M. de Castro ·
O. R. C. Busch · T. M. van Gulik · D. J. Gouma

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Abstract

Rationale Preoperative biliary drainage (PBD) has been introduced to improve outcome after surgery in patients suffering from obstructive jaundice due to a potentially resectable proximal or distal bile duct/pancreatic head lesion. In experimental models, PBD is almost exclusively associated with beneficial results: improved liver function and nutritional status; reduction of systemic endotoxemia; cytokine release; and, as a result, an improved immune response. Mortality was significantly reduced in these animal models. Human studies show conflicting results.

Findings For distal obstruction, currently the “best-evidence” available clearly shows that routine PBD does not yield the appreciated improvement in postoperative morbidity and mortality in patients undergoing resection. Moreover, PBD harbors its own complications. However, most of the available data are outdated or suffer from methodological deficits.

Conclusion The highest level of evidence for PBD to be performed in proximal obstruction, as well as over the preferred mode, is lacking but, nevertheless, assimilated in the treatment algorithm for many centers. Logistics and waiting lists, although sometimes inevitable, could be factors that might influence the decision to opt for PBD, as well as an extended diagnostic workup with laparoscopy (on indication) or scheduled preoperative chemotherapy.

Keywords Obstructive jaundice · Biliary drainage · Proximal bile duct tumor · Pancreatic head tumor

Obstructive Jaundice

Malignant disease of the extrahepatic distal (pancreatic head area) or proximal biliary tract is the most prevalent cause of obstructive jaundice, clinically evident by jaundiced skin, nausea, pruritus, dark urine and discoloration of stool, and the first presenting symptom in up to 90% of the patients. The hazardous consequence of prolonged and progressive obstructive jaundice is hepatic dysfunction due to bile stasis and cholangitis, eventually leading to hepatic failure.

In western countries, pancreatic cancer currently is the fourth cancer type for death, with an incidence of 10–15 per 100,000, whereas the reported incidence of extrahepatic cholangiocarcinoma (CCA) is approximately 1 per 100,000.¹ Radical resection of the tumor is the only possible treatment for cure. Pancreatic head tumors and distal CCA are managed by pancreatoduodenectomy (PD), while for proximal or hilar (Klatskin) extrahepatic CCA affecting the CBD, hilar resection with partial hepatectomy is indicated. Unfortunately, locoregional irresectability and/or metastatic disease, which may become apparent during preoperative work-up, preclude resection in the majority of patients.

Although the postoperative mortality after extensive hepatopancreatobiliary surgery has decreased from 20% to less than 5% in experienced centers, the overall morbidity remains high at approximately 40–60%, depending on applied definitions.^{2–6} Frequently encountered surgical complications are anastomotic leakage, in particular, pancreaticojejunostomy leakage, hemorrhage, delayed gastric emptying, and impaired wound healing. Nowadays, complications are generally managed nonoperatively, mainly

N. A. van der Gaag (✉) · J. J. Kloek · S. M. M. de Castro ·
O. R. C. Busch · T. M. van Gulik · D. J. Gouma
Department of Surgery,
Academic Medical Center at the University of Amsterdam,
Meibergdreef 9,
1105 AZ Amsterdam, the Netherlands
e-mail: D.J.Gouma@amc.uva.nl

due to an emerging role of the interventional radiologist.⁷ Nonsurgical complications consist primarily of sepsis, pneumonia, and renal disorders.

Already in 1935, this increased risk of surgery in jaundiced patients was acknowledged by A.O. Whipple, and he was the first to introduce the concept of preoperative biliary drainage (PBD) by performing a staged PD: application of a cholecystogastrostomy to reduce jaundice was followed by resection at a later stage, depending on the severity of jaundice.⁸ In the mid 1960s, a nonoperative, external drainage procedure was devised: percutaneous transhepatic cholangiography (PTC) was performed using the CIBA needle.⁹ Internal drainage came up in the seventies when the concept of endoscopic retrograde cholangiopancreatography (ERCP) was introduced. In one procedure, a diagnostic investigation was combined with a therapeutic intervention by inserting an endoprosthesis. Up to now, most patients with distal obstruction (pancreatic head/distal bile duct) are treated with ERCP, whereas in patients with proximal biliary obstruction, PTC is generally the preferred method.

The present article will focus on the role of PBD to reduce septic complications following surgery for distal and proximal biliary obstruction by considering the best evidence available in literature.

Experimental Studies

Obstructive Jaundice

Obstructive jaundice is associated with a proinflammatory state, resulting from portal and systemic endotoxemia, and experimental studies have extensively reported on the processes that are implicated in the underlying pathophysiological mechanisms; the most elucidated are discussed hereafter.^{10–12}

The endotoxin concentration in the portal circulation is increased, as a result of lack of bile salts in the gut lumen with, consequently, an unbalanced bacterial intestinal microflora and increased permeability of the intestinal mucosal barrier, promoting translocation of bacteria.^{13,14} Inadequate clearance of endotoxins in obstructive jaundice has been attributed to an altered reticuloendothelial system (RES) function of Kupffer cells in the liver.^{14,15} Recently, it has been demonstrated that, in isolated liver Kupffer cells from cholestatic mice, increased numbers of viable intracellular bacteria after infection were present, suggesting an impaired intracellular bacterial killing.¹⁶ The exact consequence with respect to development of infectious complications remains to be elucidated.

The exposure to endotoxemia and bacterial translocation due to obstructive jaundice leads to an uncontrolled induction of the inflammatory cascade: animal experiments

have shown increased concentrations of proinflammatory cytokines, such as tumor necrosis factor (TNF), IL-6, GRO/KC (IL-8), and IL-10.^{17–22} Increased concentrations of TNF, mainly produced by liver Kupffer cells, or rather, the imbalance with its soluble receptors, as antagonists and released from the cell membrane by endotoxemia, are suggested to contribute to development of complications.^{18,23} After endotoxin administration to cholestatic rats, Kennedy et al. demonstrated that blockade of Kupffer cells with gadolinium chloride leads to a lower systemic TNF activity and subsequently resulted in an improved survival.¹⁷ On the other hand, the enhanced IL-6 release, as found in jaundiced mice exposed to endotoxin, might actually play an important role in protecting the cholestatic host against hypersensitivity to endotoxin and was found to abrogate cholestatic liver injury.^{22,24} In the perspective of these results found in animal models of biliary obstruction, it appears that the generalized inflammatory state in patients with obstructive jaundice was profoundly different.²⁵ Although obstructive jaundice caused alterations in circulating concentrations of endotoxin-binding proteins, neutrophil activation and increased concentrations of IL-8, the concentrations of many of the investigated mediators in animals, such as TNF and its receptors, were not as high in patients.²⁵ Although biliary drainage did reduce IL-8 and endotoxin binding proteins, it did not change many of the mediators suggested to correlate with mortality in animal experiments.

It was demonstrated that cellular immunity, measured by the lymphocyte response to mitogens (concanavalin-A and phytohemagglutinin), was significantly lower in bile duct ligated rats but did not occur in jaundiced germ-free rats.²⁶ This would imply that hyperbilirubinemia itself does not contribute to immunosuppression, but rather, increased levels of gut-derived endotoxins due to obstructive jaundice are responsible because bilirubin levels in both conventional and germ-free bile duct ligated rats were not different. Obstructive jaundice also leads to deeply suppressed natural killer (NK) activity of nonparenchymal liver cells in rats, which can be reversed by biliary drainage of an adequate duration.^{27,28} Furthermore, the decrease in NK cell activity resulted in an enhanced growth of liver metastases, and supposedly, PBD might help to prevent liver metastases after surgery.²⁷

Next to an increased risk for development of infectious complications, obstructive jaundice has been associated with renal dysfunction, with its extent depending on the intensity of biliary obstruction.^{10,29,30} In the pathogenesis of renal failure, extracellular volume depletion may be an important factor, and while the observed increases in plasma renin and aldosterone are logical endocrine responses to a reduced extracellular water compartment, there also is a paradoxical rise in plasma atrial natriuretic

peptide (ANP) in response to biliary obstruction.³¹ The raised plasma ANP level might be the result of the passage of bile components to the blood and is reversed to basal levels after biliary drainage, thereby improving renal dysfunction.^{31,32} Furthermore, myocardial dysfunction in obstructive jaundice has been suggested to be the consequence of hemodynamic disturbances due to altering ANP concentrations, while after biliary drainage, a correlation was found between decreasing ANP concentrations and increasing cardiac output.³³

Biliary Drainage

Biliary drainage as a therapeutic method to reduce postoperative septic complications has been shown in multiple experimental models to improve liver function, nutritional status, and cell-mediated immune function; to reduce systemic endotoxemia and cytokine release; and, subsequently, to improve overall immune response.^{20,26,34–38} Mortality was significantly reduced in these animal models. With respect to the preferred route of drainage, internal PBD was found to be superior to external PBD in terms of reduction in endotoxemia and mortality by some, whereas others demonstrated external drainage, although in the short-term, to lead to a better recovery of cellular immunity than internal drainage.^{34,39,40} In jaundiced rats undergoing hepatectomy, both external and internal PBD improved serum liver function tests; however, a better liver regeneration and function after hepatectomy was observed after internal drainage.⁴¹

A negative side-effect of biliary drainage is the associated complications of the procedure itself. In dogs, insertion of biliary endoprotheses resulted in bile contamination and severe chronic inflammation of the bile duct.⁴² This inflammatory process led to considerable thickening of the wall in both normal and obstructed bile duct, with transmural, fibrosing inflammation and, occasionally, ulceration. Two months after removal of the endoprosthesis, bacterobilia persisted and the bile duct remained inflamed and dilated, albeit less severe. To put an endoprosthesis in the bile duct before surgery resulted in higher postoperative infectious complications, an increased risk of anastomotic dehiscence, more frequent leakage of infected bile, and increased abscess formation. It is likely that the infected bile and the condition of the bile duct wall, as a consequence of the preoperative stenting, were responsible for these complications.

Concerning the duration of PBD, it has been suggested that adequate recovery of hepatic function depends on the duration of biliary decompression and duration of obstructive jaundice before decompression.⁴³ A minimum of 4–6 weeks of preoperative drainage was advised, with even longer periods proposed for patients with a prolonged

biliary obstruction before decompression. A more recent study showed that preoperative decompression is necessary for at least 3 weeks before coagulation and hepatic and RES function start improving.⁴⁴

PBD for Distal Obstruction

Patients suspected to have a tumor in the pancreatic head area (pancreas, distal bile duct, papilla of Vater), without radiological evidence of irresectability, will undergo an exploration with the intention of resection of the tumor. In the preoperative course, a majority of these patients suffer from symptomatic obstructive jaundice.

For many decades, diagnostic strategies comprised the performance of an ERCP in patients with obstructive jaundice, accompanied in most cases with stent placement for PBD as a therapeutic measure for relief of symptoms. Nowadays, state-of-the-art radiological techniques offer a higher diagnostic accuracy than ERCP, require a minimum amount of time, are noninvasive, and have the advantage of assessing local tumor extension, as well as distant metastases.^{45–47} Therefore, ERCP as a diagnostic tool is considered obsolete in many countries, although geographical differences do exist. Implementation of a strategy without diagnostic ERCP is not generally adapted yet in The Netherlands; a survey revealed that, prior to referral for further assessment and (surgical) treatment at the tertiary center, almost 40% of patients already had ERCP performed, primarily as a diagnostic procedure.⁴⁸

The therapeutic effect of PBD, either by means of ERCP or PTC, has been extensively debated throughout the past few decades. One of the largest prospective randomized trials performed in the USA by Pitt et al. concluded that PBD does not reduce operative risk; however, it increases hospital cost and, therefore, should not be performed routinely.⁴⁹ A systematic review from our institution summarized all retrospective and prospective studies, published between 1966 and 2001, with the aim to evaluate the efficacy of drainage in jaundiced patients, compared to patients that underwent direct surgical treatment.⁵⁰ Outcome measures of the meta-analysis were in-hospital death rate, overall complications resulting from the treatment modality (PBD- and surgery-related complications), and hospital stay. Five randomized controlled studies comprising 302 patients (level I evidence) and 18 cohort studies comprising 2,853 patients (level II evidence) met inclusion criteria and were analyzed. Meta-analysis for both level I and level II studies showed no difference in mortality between patients who had PBD and those who had surgery without PBD. However, overall complication rate was significantly adversely affected by PBD compared with surgery without PBD; for level I, they were 57% and 42%,

respectively, indicating a relative risk reduction of 15% and an absolute risk reduction of 27% in case surgery would be performed without PBD. Analysis of level II studies showed equal numbers. If PBD had been without complications, the complication rate would be in favor of PBD based on level I studies, and without difference based on level II studies. Further, overall hospital stay was prolonged after PBD. In all it, was concluded that the potential benefit of PBD, in terms of postoperative rates of death and complications, does not outweigh the disadvantage of the drainage procedure and therefore should not be performed routinely, unless further improved PBD techniques would become available.

The inverse relationship between the institutional volume of major oncological surgery and the resulting morbidity and mortality rates is well recognized and the key reason for a plea for centralization of complex surgical procedures.^{4,51} Pisters et al. brought this argument up to justify PBD to create time for referral of patients to high-volume tertiary surgical centers, their (retrospective) study did not demonstrate an increase in the risk of major postoperative complications associated with PBD and stent placement.^{52,53} Logistics in terms of (local) referral patterns, waiting lists, extended diagnostic workup with laparoscopy (on indication), or scheduled preoperative chemotherapy could be other plausible factors that might influence the decision to opt for PBD. Possibly, these factors are region-specific for, at least in the USA, in the eastern part of the country, early surgery without drainage is strongly advocated, whereas in the southern part, PBD is favored.⁵³ However, ideally, such logistic arguments should never be decisive in treatment consideration. Furthermore, even in high case-load centers, a hospital volume-outcome effect for ERCP and stenting exists, which should be taken into account in the discussion of whether or not to start with ERCP and drainage before referral.^{54,55}

It should be mentioned that the prospective studies included in our meta-analysis largely consisted of a suboptimal design, while they were not carried out according to the basic principles of clinical trial reporting (the CONSORT statement).⁵⁶ Various (outdated) forms of internal and external drainage procedures for both proximal and distal obstruction were included, different durations of drainage were used, and different surgical procedures were followed. These possible methodological and reporting deficiencies might hamper drawing conclusions. Furthermore, due to the time span of included studies, outmoded PBD techniques and materials inevitably add significantly to the negative outcome of drainage.

Therefore, we have conceived a large randomized controlled multicenter trial (in patients needing a PD, distal obstruction) to obtain the highest level of evidence by comparing a “PBD strategy” (standard strategy) with that of

an “early-surgery” strategy: the drainage vs. operation (DROP) trial.⁵⁷ Primary outcome measure is the incidence of overall severe complications; secondary outcome measure includes hospital stay, number of invasive diagnostic tests, costs, and quality of life.

PBD for Proximal Obstruction

Hilar CCA remains one of the most difficult tumors in terms of staging and radical treatment.⁵⁸ Furthermore, the correct mode of preoperative management is still under debate.^{59,60} Most patients with hilar CCA show liver dysfunction caused by obstructive jaundice, which has proven to be a significant risk factor in major liver resection.^{61–63}

As mentioned earlier, animal studies concerning PBD are convincing in terms of complication reduction; clinical studies report conflicting results.^{64–67} Two randomized controlled trials, in which a PBD strategy was compared to early-surgery strategy in jaundiced patients, including patients with proximal lesions, did not display a difference in perioperative mortality; however, they encountered a high rate of PBD-procedure-related complications.^{68,69} Cautious interpretation is warranted as these studies used outdated techniques; included a variety of causes of biliary obstruction; and, moreover, comprised only a limited number of patients with proximal CCA. A prospective cohort study found a significantly higher rate of infectious complications if PBD was applied, whereas another study concluded that routine use of PBD was not justified since mortality was not significantly different and recovery of hepatic synthetic function was identical to that of non-jaundiced patients.^{70,71}

In contrast, Japanese literature is unanimous in advising and emphasizing the benefit of PBD.^{72–74} The postoperative mortality rates after major liver resections performed for hilar CCA in Japan are low, currently between 0% and 9%, for which many consider PBD to be an essential element in preoperative management.^{73–76} Most centers agree that, for tumors requiring extensive liver resection, biliary drainage of at least the future remnant liver is necessary to prevent hepatic failure.⁷⁷ With the introduction of preoperative portal embolization, to induce hypertrophy of the future remnant liver, the application of wider resection margins and the development of new endoscopic techniques are other factors that have led to a favorable attitude for a preoperative drainage strategy.⁷⁸

The technique of PBD for proximal obstruction, as well as which part of the liver should be drained, is an ongoing controversy. External drainage by PTC is traditionally the preferred method for relief of obstructive jaundice due to proximal obstruction. Endoscopic biliary drainage, al-

though a less invasive technique, carries the increased risk of developing cholangitis due to bacterial contamination from the duodenum.⁷⁸ Moreover, endoscopic biliary drainage implicates total biliary drainage (TBD) (entire liver), or at best, hemihepatic drainage by left or right hepatic duct drainage, whereas drainage via PTC offers the possibility to perform more selectively segmental drainage. An argument for selective biliary drainage (SBD) is the subsequent induction of hypertrophy of the future remnant liver and atrophy of the future resected part of the liver.^{79,80} A retrospective cohort study investigated 42 consecutive patients who underwent SBD or TBD before hepatectomy.⁸¹ SBD was found not to increase the risk for cholangitis, compared with TBD. In association with portal vein embolization, SBD was superior to TBD in promoting hypertrophy of the future remnant liver, whereby extended hemihepatectomy could be performed more safely. Although not in the perspective of PBD, the only existing prospective randomized controlled trial comparing TBD vs. SBD appointed patients with unresectable hilar bile duct tumors to undergo either unilateral or bilateral endoscopic hepatic duct drainage.⁸² Unilateral drainage resulted in a higher technical success rate of stent insertion and a significantly lower incidence of complications, mainly early cholangitis.

In spite of the presumed advantages of PTC drainage over endoscopic drainage, it should be noted that no clinical randomized controlled trials exist regarding the most optimal route of drainage in terms of complication reduction and patient burden. Currently, the preferred technique of biliary drainage prior to surgery for a proximal bile duct tumor depends mainly on local expertise.

Summary and Conclusion

Obstructive jaundice is the most prevalent symptom in potentially resectable distal and proximal lesions of the extrahepatic biliary tract/pancreatic head area. The presence of toxic substances such as bilirubin and bile salts, impaired liver function, and altered nutritional status due to obstructive jaundice have been characterized as factors for the development of complications. Whereas PBD was to yield beneficial effects in experimental models, conflicting results have been observed in human studies. For distal obstruction, currently, the “best evidence” available clearly shows that PBD should not be performed routinely. Unfortunately, most of the available data are outdated, and hopefully, the large prospective randomized controlled DROP trial will solve the dilemma of whether or not PBD, as an additional procedure, improves surgical outcome to such an extent that postponement to resection of progressive malignant disease is justified.⁵⁷ The highest level of evidence for PBD to be performed in proximal

obstruction, as well as over the preferred mode, is lacking but, nevertheless, assimilated in the preferred treatment algorithm for many centers. Logistics pose an undesirable, although sometimes inevitable, argument to perform PBD.

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