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Pre-operative stenting is associated with a higher prevalence of post-operative complications following pancreatoduodenectomy

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ABSTRACT

Objectives: Whilst there are theoretical benefits from pre-operatively draining the biliary tree prior to pancreatoduodenectomy (PD), the current literature does not support this intervention. The aim of this study was to explore the relationship between pre-operative stenting, bactibilia and outcome in a large United Kingdom tertiary referral practice.

Methods: Patients undergoing PD were identified from a prospectively maintained database. The presence or absence of a stent prior to PD, and the results of bile cultures taken at PD were related to the subsequent post-operative course and the development of complications.

Results: 280 patients underwent PD for periampullary malignancies, all of whom presented with jaundice. 118 patients were stented prior to referral (98 ERCP, 20 PTC). Bile cultures were positive more frequently in the stent group (83% *vs.* 55%; $p = 0.000002$) and bactibilia was more common after ERCP than PTC (83% *vs.* 56%; $p = 0.006$). The overall prevalence of complications was 54% in the stented and 41% in the non-stented group ($p = 0.03$) with statistical significance achieved for pancreatic leak ($p = 0.013$) and haemorrhagic complications ($p = 0.03$). Comparing stent with no stent, there as no difference in the 30-day mortalities (8.5% vs. 6.8%; $p = 0.6$) or the 1-year mortality rates (35% vs. 28%; $p = 0.21$). Mortality rates in the infection *versus* no infection groups were comparable at 30 days (8.5% vs. 5.5%; $p = 0.21$), and at 1 year (30.7% vs. 26.4%; $p = 0.25$).

Conclusions: Pre-operative stent insertion prior to PD is associated with increased morbidity but not mortality and this is greatest for stents placed at ERCP.

1. Introduction

There is considerable debate as to the management of the jaundiced patient with a pancreatic adenocarcinoma who is a candidate for pancreatoduodenectomy (PD). There is experimental evidence that biliary drainage improves nutritional status, reduces the risk of endotoxaemia, and may improve immune function[1,2,3], although this has yet to be extrapolated to the clinical setting. There is in addition literature demonstrating that jaundice increases the prevalence of post-operative complications such as: anastomotic leak rates; secondary haemorrhage; and post-operative renal failure[4] and as such pancreatic resection should be avoided until adequate decompression is achieved.[5] There is also recent evidence from a clinical study that despite the impaired synthesis of vitamin k dependent clotting factors in patients with biliary obstruction, jaundice is associated with a pro-coagulant state which is reversed by stenting.[6] Indeed, in his original description, Whipple described his operation as a 2-stage procedure specifically for this purpose.[7]

However, the potential benefits of decompression through stenting of the biliary tree have to be balanced by the morbidity associated with the procedure and effects that stenting may have on subsequent resection. There is no doubt that stenting in the presence of jaundice is associated with a significant morbidity, some of the more important complications being: haemorrhage; pancreatitis; and stent occlusion[8] which occur in up to 50% of cases as a result of the development of a biofilm[9] leading to recurrent jaundice and subsequent cholangitis. One other important statistic that is not evident from the literature is the number of patients who are stented in the presence of a resectable tumour but suffer significant morbidity and are then deemed no longer suitable candidates for surgery.

Contemporary data from renowned pancreatic institutions have published large cohort studies all of which suggest that stenting is

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of no benefit[10–16] Indeed, many authors noted stenting to be associated with increased morbidity, and in some cases mortality. Surprisingly, there are only 2 adequately powered randomised trials comparing internal biliary drainage followed by surgery with surgery alone.[17,18] In the more recent of the trials, van der Gaag and colleagues studied 202 patients, 96 of whom were randomised to surgery and 106 to stenting prior to surgery.[18] They found the overall complication rates to be 39% in the former and 74% in the later group with morbidity attributed to stenting in 37% and to the resection in 47%. Furthermore, three meta-analyses have recently been published all of which concluded that pre-operative biliary drainage offers no benefit and as such should not be performed routinely.[14,19,20]

The aim of this study was to assess the morbidity and mortality associated with biliary stenting in a population of patients with malignant periampullary cancers referred to a specialist pancreatic tertiary referral centre.

2. Patients and methods

Consecutive patients undergoing PD for malignant disease were identified from a prospectively maintained departmental database. Patients undergoing resection of benign disease and malignant disease affecting the body and tail of the pancreas were excluded. Data were reviewed to identify those stented and those in which a stent was not placed prior to PD.

For patients stented prior to PD, the type of procedure – internal drainage via endoscopic retrograde cholangio pancreatography (ERCP) or external drainage by means of percutaneous transhepatic cholangiography (PTC) was noted as was the interval between stenting and surgery. All stents used were polyethylene and were either size 10 or 12 French.

The effectiveness of the stenting procedure in relieving biliary obstruction was assessed through estimation of pre-operative bilirubin and alkaline phosphatase levels. And pre-operative white cell count was assessed as a marker of infection.

Antibiotic prophylaxis consisting of a second generation cephalosporin and metronidazole were administered on induction of anaesthesia and were continued for 2 doses post-operatively.

All patients had cultures taken directly from the bile at the time of surgery, and where present, the proximal ends of biliary stents were also cultured. Adjustments to antibiotic therapy were made in accordance with culture results.

Post-operative complications were documented including: biliary and pancreatic leaks; septicaemia; gastrointestinal or intra-peritoneal haemorrhage; cardiac arrhythmia/acute coronary syndrome; pneumonia/respiratory failure; renal failure; and death.

A bile leak was defined as the presence of bile in the drain after the second post-operative day whilst a pancreatic leak was defined as the presence of amylase rich fluid (>5000 IU/L) in the drain after post-operative day 5. Infectious complications were diagnosed on the basis of localized or systemic symptoms and signs, and confirmed by culture, with radiological investigations where indicated to localize the source. Haemorrhagic complications were identified on the basis of haemodynamic instability, overt blood loss or the requirement for transfusion with the source being confirmed by endoscopic or radiological means. Documentation of cardiac and respiratory complications was based on clinical findings confirmed by electrocardiography and radiology with additional biochemical and microbiological tests where appropriate. Renal impairment was defined on the basis of deterioration in renal function with or without the requirement for renal support. The mortality was taken to be a 30-day post-operative mortality and in addition the number of patients surviving 1-year was also documented.

The subsequent post-operative courses and the development of complications were related to the presence or absence of stents and identification of infected bile.

The results were expressed as median with ranges in parentheses, and in case of complications, number experiencing the complication with percentages in parentheses. Analyses performed included the prevalence of complications in: stent *versus* no stent; infection *versus* no infection; and the varying combination of infection ± stent.

All statistical analyses were performed using the SPSS for Windows™ version 14.0 (SPSS Inc, Chicago, Ill, USA), and statistical significance was taken at the 5% level.

3. Results

In the period covered by the study, 280 patients presenting with jaundice underwent PD for malignancies obstructing the distal bile duct all of which underwent surgery with curative intent. There were 128 females and 152 males and the median age was 65.6 years (Range: 21.7–83.0 years).

The histological types of the obstructing malignant tumours in order of frequency were: pancreatic adenocarcinoma ($n = 148$); ampullary carcinoma ($n = 77$); cholangiocarcinoma ($n = 25$); duodenal adenocarcinoma ($n = 21$); acinar cell carcinoma ($n = 3$); cystic carcinoma ($n = 2$); adenosquamous carcinoma ($n = 1$); spindle cell carcinoma ($n = 1$); pseudo-papillary cystic carcinoma ($n = 1$) and anaplastic carcinoma ($n = 1$). There were more duodenal tumours in the non-stented group 19 *vs*. 2 but all other pathological types shared a comparable distribution. Two hundred and fifty nine were pylorus preserving pancreatoduodenectomies (PPPD) and 21 were classical Whipple's operations.

A stent had been placed in 118 patients prior to referral to the unit of which, 98 were placed at ERCP and 20 at PTC. Despite stenting, the percentage of patients with a normal bilirubin level or alkaline phosphatase at the time of PD were comparable for stented and non-stented groups at (38.1% *vs*. 42%, $p = 0.46$) and (1.7% *vs*. 3.4%, $p = 0.45$) respectively. There was however a significant difference in the mean bilirubin (98 *vs*. 130 μmol/L; $p = 0.032$) and alkaline phosphatise (664 *vs*. 709 IU/L; $p = 0.046$) in the stented group when compared to the non-stented cohort. There was no difference in the mean white cell count between patient groups at (8.4×10^9 vs. 8.9×10^9; $p = 0.14$).

The interval from referral to surgery in the surgery alone group was a median of 5 days (Range: 2–13) and from stenting to surgery was 23 days (Range: 8–43 days).

Pre-operative cultures of bile ± biliary stents were positive significantly more frequently in the stent group at 98/118 compared with the no stent group 91/162 (83% *vs*. 56%; $p = 0.000002$). Furthermore, a positive culture was obtained significantly more frequently following stenting performed at ERCP than PTC (83% *vs*. 55%; $p = 0.006$). In the ERCP group, 33 of 81 cases of infected bile grew a single organism and in the remainder cultures were polymicrobial whilst in the PTC group, 64% of cultures were monomicrobial and 36% grew multiple organisms ($p = 0.15$).

The organisms identified from culture of the bile and stent tip are summarised in Table 1. There were a wide variety of organisms but no significant differences were identified between the groups. A growth of *Candida* species was the single most common isolate being identified in 43/189 (22.8%) of patients with a positive culture.

Complications for patients receiving a stent *versus* no stent are summarised in Table 2. The overall prevalence of complications was 54% in the stented and 41% in the non-stented group ($p = 0.03$). The prevalence of all complications except for cardiac were more common in the cohort receiving a stent, with statistical significance

Table 1
Organisms cultured from bile and/or stents of patients with and without stents inserted prior to pancreatoduodenectomy.

Organism	Stent	No stent
Candida species	25	18
Enterococcus species	23	15
Mixed coliforms	16	19
Klebsiella species	19	10
Eschericha coli	16	6
Enterobacter species	12	7
Alpha-haemolytic *Streptococci*	5	6
Citrobacter species	6	2
Staphylococcus aures	4	1
Serratia species	4	1
Clostridium perfringens	3	1
Beta-haemolytic *Streptococci*	2	1
Bacteroides species	0	2
Staphylococcus epidermidis	1	1
Stenotrophomonas maltophilia	1	0
Lactobacillus species	1	0
Hafnia alvei	1	0
Pseudomonas species	1	0
Acinetobacter species	0	1

achieved for pancreatic leak ($p = 0.013$) and haemorrhagic complications ($p = 0.03$). An analysis of presence of infection *versus* no infection (Table 3.) revealed the prevalence of wound complications as the only significant difference, with significantly more wound infections in those with infected bile.

Further analysis incorporating stents and infections into 4 groups namely: infection and stent; infection but no stent; stent but no infection; and no stent or infection (Table 4) revealed no significant differences between any of the groups for any of the complications.

In 68% of cases in which a post-operative infective complication occurred, the causative organism was the same as identified from the peri-operative bile culture.

There were no differences in the 30-day mortality at 8.5% vs. 6.8% ($p = 0.6$) or the 1-year mortality at 35% vs. 28% ($p = 0.21$) when comparing stent to no stent insertion. Furthermore, mortality rates in the infection *versus* no infection groups were comparable at 30 days at 8.5% vs. 5.5% ($p = 0.21$), and at 1 year at 30.7% vs. 26.4% ($p = 0.25$).

4. Discussion

The primary finding of the study was that pre-operative biliary stenting was not beneficial in terms of either morbidity or mortality for patients undergoing PD, and indeed was associated with increased risk for pancreatic leak as well as gastrointestinal and intra-peritoneal bleeding. These figures are in keeping with the published body of evidence that has found no benefit to pre-operative stenting [10–20]. Proponents of stenting may argue that the lack of a detrimental effect from stenting was a good thing however, contrary to this is the argument that if a procedure with a recognised side-effect profile is to be performed then there needs to be evidence of a beneficial outcome. In this study, the prevalence of infection was greater in the stented group and the patients being stented suffered more pancreatic leaks and haemorrhagic complications than the non-stented patients. We would therefore be against routine stenting.

There was no difference in the rates of infective complications between the stent and no stent groups. This is understandable as the source of the infection was the bile itself. In all cases the bile duct is clipped following division to prevent bile leakage into the peritoneal cavity during the reconstruction. As a result of this manoeuvre, there is less opportunity for bacterial contamination of the retroperitoneum or abdominal wall and hence of infection.

One aspect that cannot be fully assessed in a study as such this is the full extent of the morbidity and mortality from stenting. ERCP and stenting, the more common means of drainage, is associated with a morbidity of 1–25% including: bleeding; pancreatitis; cholangitis; and perforation; together with a mortality of 0.2–1% and a failure rate of 3–30%[23] and it may be that some potentially resectable patients may not have been resected as a result of suffering these complications.

Despite the bilirubin being lower in the stented group, the majority of patients did not have normal bilirubin or alkaline phosphatise levels indicating that the stents were not draining adequately. This may be related to delays between presentation and surgery, however this was only a median of 23 days for the patients undergoing stenting, and literature would suggest that plastic stents should remain patent for between a median of 62–165 days.[24] Another possibility, often overlooked, may be the formation of delta-bilirubin, as the binding of bilirubin to plasma proteins such as albumin prolongs its half life and delays the resolution of jaundice.[25] The percentage of delta-bilirubin increases with the duration of jaundice. A further option is that the clinical histories prior to presentation, diagnosis and referral may have been significantly longer than indicated in the case notes but this is impossible to confirm in a retrospective study.

Table 2
Comparison of complication rates in patients with and without stents present at time of pancreatoduodenectomy.

Complication	Stent ($n = 118$)	No stent ($n = 162$)	Chi-square (p value)
Pancreatic leak	26 (22%)	18 (11.1%)	6.15 (0.013)
Bile leak	4 (3.4%)	4 (2.5%)	0.21 (0.65)
Septicaeimia	16 (13.6%)	15 (9.3%)	1.28 (0.25)
Intra-abdominal abscess	10 (8.5%)	10 (6.2%)	0.55 (0.46)
Gastrointestinal/ Intra-abdominal haemorrhage	15 (12.7%)	9 (5.6%)	4.46 (0.03)
Wound infection/ dehiscence	22 (18.6%)	20 (12.3%)	2.12 (0.15)
Cardiac arrhythmia/ acute coronary syndrome	9 (7.6%)	18 (11.1%)	0.95 (0.33)
Pneumonia/ respiratory failure	15 (12.7%)	14 (8.6%)	1.2 (0.27)
Renal Failure	11 (9.3%)	7 (4.3%)	2.8 (0.08)

Table 3
Complication rates following pancreatoduodenectomy in relation to the presence or absence of infection.

Complication	Infection ($n = 189$)	No infection ($n = 91$)	Chi-square (p value)
Pancreatic leak	31 (16.4%)	13 (14.3%)	0.21 (0.65)
Bile leak	6 (3.2%)	2 (2.2%)	0.24 (0.63)
Septicaeimia	22 (11.6%)	9 (9.9%)	0.19 (0.66)
Intra-abdominal abscess	12 (6.3%)	8 (8.8%)	0.55 (0.46)
Gastrointestinal/ Intra-abdominal haemorrhage	16 (8.5%)	8 (8.8%)	0.008 (0.9)
Wound infection/ dehiscence	35 (18.5%)	7 (7.7%)	5.6 (0.02)
Cardiac arrhythmia/ acute coronary syndrome	22 (11.6%)	5 (5.5%)	2.66 (0.1)
Pneumonia/respiratory failure	19 (10.1%)	10 (11%)	0.06 (0.81)
Renal Failure	11 (5.8%)	7 (7.7%)	0.36 (0.55)

Table 4
Combined effects of stenting and biliary infection on complication rates following pancreatoduodenectomy.

Complication	Stent -ve infection -ve ($n = 71$)	Stent + ve infection -ve ($n = 20$)	Stent -ve infection + ve ($n = 91$)	Stent + ve infection + ve ($n = 98$)	Chi-square (p value)
Pancreatic Leak	9 (12.7%)	4 (20%)	9 (9.9%)	2 (22.4%)	6.45 (0.99)
Bile leak	1 (1.%)	1 (5%)	3 (3.3%)	3 (3.1%)	0.95 (0.81)
Septicaeimia	6 (8.5%)	3 (15%)	9 (9.9%)	13 (13.3%)	1.42 (0.70)
Intra-abdominal Abscess	4 (5.6%)	3 (15%)	6 (6.6%)	6 (6.1%)	2.36 (0.50)
Haemorrhage	5 (7%)	3 (15%)	4 (4.4%)	12 (12.2%)	5.0 (0.17)
Wound Complications	5 (7%)	2 (10%)	16 (17.6%)	19 (19.4%)	5.87 (0.12)
Cardiac Complications	5 (7%)	0 (0%)	13 (14.4%)	9 (9.2%)	4.96 (0.17)
Respiratory Complications	7 (9.9%)	3 (15%)	7 (7.7%)	12 (12.2%)	1.56 (0.67)
Renal Failure	4 (5.6%)	3 (15%)	3 (3.3%)	5 (5.1%)	4.45 (0.22)

The presence of infection as indicated by bactibilia at the time of surgery, was seen more commonly in the stent group, however, bacteria were cultured from the bile of 55% of patients without a stent present. This is keeping with the observation that obstructive jaundice is a significant risk factor for the development of bactibilia and subsequent cholangitis.[26] Stenting further increases this risk[27] by providing an environment for the development of a bacterial biofilm.[9]

The same organisms identified within the bile culture at the time of PD were responsible for subsequent infection in 68% of patients developing an infective complication. This figure is in keeping with the published literature where the organism isolated from bile has been linked to subsequent infection in 50–100% of cases [10,11,25–28]. In patients not manifesting identical organisms, the infection may have occurred *de-novo* following alteration of microbial flora due to standard cephalosporin and metronidazole. Interestingly, of 179 patients with bactibilia, *Candida* species were identified in 43 cases and although antibacterial prophylaxis is administered, anti-fungals are not routinely prescribed. The importance of *Candida* is variable in the literature, and whilst some studies report the fungus as a common finding, others such as Isla et al., identified *Candida* in only 1% of cultures.[27]

The insertion of biliary drainage catheters prior to referral is not unique to this series, and was reported as a major problem by Cortes et al.[28] who noted this to be the case in 79% of cases. One of the main problems with assessing pre-operative stenting is the lack of standardisation for stenting, with some interventional endoscopists inserting stents for all patients suspected of having a tumour prior to staging. In such cases imaging with both computed tomography and endoscopic ultrasound may be compromised. In addition there is no standard bilirubin level at which stenting is advocated and most surgeons do not have a threshold above which they insist on stenting. In an elegant study, Mansfield et al., examined bilirubin levels at presentation in their patients with pancreatic and periampullary malignancies and then followed subsequent increases in bilirubin until relief of jaundice.[25] The median bilirubin at presentation in a series of 111 patients was 160 μmol/L. The bilirubin levels increased at a median increase of 13.1 μmol/L per day. It took 3, 13, 22 and 31 days respectively for the bilirubin to reach 200 μmol/L, 300 μmol/L, 400 μmol/L and 500 μmol/L thus indicating a window of opportunity for referral and surgery without the need for drainage. Thus if a threshold of 300 μmol/L is accepted then the surgeon has 2 weeks to stage and operate upon the patient.

One interesting finding was the identification of a higher infection rate in patients undergoing ERCP compared with PTC. This is particularly interesting since most patients now undergoing PTC do so after failed ERCP, and only a small minority would undergo primary PTC due to unfavourable anatomy. Furthermore the literature would suggest that growth seen in undrained and PTC patients is usually mono-microbial whereas that in patients with a stent placed at ERCP is usually polymicrobial.[29] In this series 64% of PTC cultures were mono-microbial whereas for the ERCP group the figure was only 41%.

A potential criticism of the study is that we did not use the current definition of a pancreatic fistulas as suggested by Bassi and colleagues.[30] However, this definition was accepted by the HPB community after the commencement of the current study. Prior to this there were numerous different definitions in the literature[31] and our database was designed with the drain amylase of >5000 IU/L on day five as the criteria for meeting the diagnosis of pancreatic leak.

One area in which selective stenting may be of importance is in relation to neoadjuvant therapy. As the evidence for such therapy increases, there may be a need for stenting with metallic stents as the interval between diagnosis and surgery may be 3–4 months.[32,33] There is good data to suggest that metallic stents are more efficacious than plastic stents[34] and do not compromise subsequent resections.[12]

5. Conclusions

Pre-operative stent insertion prior to PD is associated with increased morbidity which is greatest for stents placed at ERCP. The risk is present at 30 days and persists at 1 year. Efforts should be made to refer for consideration of resection prior to stenting of the biliary tree. Furthermore, bile cultures should be taken routinely and infections treated appropriately, as biliary infection is also associated with increased morbidity independent of stenting.

Ethical approval

Ethical approval was not sought for this case series as it was not deemed necessary. However, the database from which the data was extracted is covered by research and development department approval.

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Conflict of interest

None to declare.

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