Palliation of Malignant Biliary Obstruction: Adverse Events are Common after Percutaneous Transhepatic Biliary Drainage

P. A. Heedman, E. Åstradsson, K. Blomquist and Rune Sjödahl

The self-archived postprint version of this journal article is available at Linköping University Institutional Repository (DiVA):
http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-147587

N.B.: When citing this work, cite the original publication.

Original publication available at:
https://doi.org/10.1177/1457496917731192

Copyright: SAGE Publications (UK and US)
http://www.uk.sagepub.com/home.nav
Palliation of malignant biliary obstruction. Adverse events are common after percutaneous transhepatic biliary drainage.

Short title: Palliative transhepatic biliary drainage

P-A Heedman1,2, E Åstrandsson3, K Blomquist4, R Sjödahl4,5

1 Unit of co-ordinated cancer investigation, University hospital, Linköping, Sweden
2 Palliative Education and Research Center, Östergötland, Sweden
3 Unit of palliative care, Department of Specialized home care, Region of Östergötland, Linköping, Sweden
4 Department of Surgery, University hospital, Linköping, Sweden
5 Department of Clinical and Experimental Medicine, Linköping University, Sweden

Correspondence:
Senior Professor
Rune Sjödahl, Department of Surgery, University Hospital, SE-581 85 Linköping, Sweden
Telephone number: +703 969845
e-mail: Rune.sjodahl@regionostergotland.se

Acknowledgement. We want to thank Victoria Fomichev, Regional Cancer Center southeast region, Sweden, for statistical advice

Conflicting interests: none

Funding: none
Abstract

Background and aims. To alleviate symptoms of biliary obstruction due to malignant disease endoscopic stents in the common bile duct is the first choice. When endoscopic stenting fails in palliative patients one option is to use a percutaneous biliary external drainage (PTBD) but it is not clear whether and how it can reduce the symptom load. The aim of this study was to evaluate benefits and disadvantages of PTBD in palliative care.

Material and Methods. Inclusion criteria were malignant disease and bilirubin ≥26 ummol/L in plasma. A structured protocol was used from the last CT-scan before the PTBD and during 14 days afterwards.

Results and Conclusions. Inclusion criteria were fulfilled in 140 patients. Median age was 70 years (33-91). Some 126 patients had a remaining external PTBD. Jaundice was the initial symptom in 62 patients (44 %). Within the first week after PTBD the bilirubin decreased from 237 umol/L (31-634) to 180 umol/L (17-545). Only 25 % reached a level below the double upper reference value. Pruritus occurred in 27 % before the PTBD but the bilirubin value did not differ from patients without pruritus. However, the pruritus was relieved in 56 %. Antibiotic prophylaxis protected to some extent from infectious complications. Adverse events were common and early mortality was high (16 % within 14 days). Jaundice should not by itself be an indication for PTBD for palliation except when the aim is to prepare the patient for chemotherapy. PTBD was associated with a high early mortality as well as other frequent and severe adverse events. It is mandatory that the patients are informed carefully about what can be expected regarding the positive effects and the risks of adverse events.

Key words: hyperbilirubinaemia, jaundice, malignancy, palliation, biliary obstruction, transhepatic drainage, outcome
Introduction

In biliary obstruction due to malignant disease, liver metastases, other distant metastases or locally advanced tumour growth are common. The obstruction is associated with various manifestations as jaundice, pruritus, altered taste of food, anorexia, malnutrition, renal impairment, impaired immune dysfunction (1, 2, 3) and impaired quality of life (4, 5). For a long time the relief of obstructive jaundice was surgical bilioenteric bypass (6-7) but since several decades percutaneous transhepatic biliary drainage (PTBD) or endoscopic drainage are less invasive alternatives. Endoscopic stents in the common bile duct is today the first choice to alleviate symptoms and prolong life by decreasing hyperbilirubinemia before surgery, chemotherapy, or as palliation (8). However, when endoscopic stenting fails in palliative patients one option is to recommend PTBD and another is to offer best supportive care. The risks for complications should be limited in palliative care as the main purpose is to preserve or improve quality of life, and sometimes to prolong life. It is, however, not clear whether and how a remaining external drainage can reduce the symptom load in palliative patients. The aim of this study was to evaluate the benefits and the disadvantages of PTBD in palliative care.

Material and methods

Procedures related to percutaneous transhepatic cholangiography (PTC) were performed in 516 patients during June 2010-June 2013 at Linköping University hospital. All procedures were identified from the hospital registration systems. Inclusion criteria in this study were patients with malignant disease and bilirubin ≥26 umol/L in plasma. All PTBD procedures were done in general anaesthesia, the classification according to ASA is shown in table 1. All included patients had stage IV disease and received palliative treatment without surgery. In 68 patients an ERCP with or without successful endoscopic drainage had been performed.
previously. When possible, the external drainage was converted to an internal drainage. An intention to internal stenting in this patient cohort with advanced diseased was documented in 31 patients and became permanent in 14 patients. The flow chart of patients is shown in figure 1. Digital medical records of the patients included were reviewed using a structured protocol from the last CT-scan before the PTBD until 14 days after the PTBD. In addition to age and gender the protocol included cancer diagnosis, symptoms (lack of appetite, fatigue, pruritus, dark urine, weight loss, abdominal pain, feeling of sickness), performance status, ASA, date of PTBD, antibiotics, kind, time, and duration of complications, effect on symptoms, and various laboratory values.

MRI was used to determine the level of biliary obstruction and to assess the amount of functional liver parenchyma that could be drained. Puncture of the bile ducts close to the liver hilus was guided by ultrasound. Radiological classification of the biliary obstruction was discussed in separate sessions until consensus was obtained. It comprised intrahepatic, extrahepatic, and combined intra- and extrahepatic obstruction.

Ethics. This report was part of a quality control and written permission to the study design was given by the chairman at the Department of Surgery, Linköping University hospital (dnr CKOC-2014-00172).

Statistical analysis. Differences between patient groups were tested with a Z-test and comparisons of the distribution between the different groups with a two-sided chi-squared test both taking a p-value of 5 % as significant.

Results.
Manifest or suspected malignant disease and bilirubin ≥26 umol/L in plasma was identified in 140 patients (75 males, 65 females). The median age was 70 years (range 33-91) (table 1). Sixty-seven percent had ASA classification II-III. Some 126 patients continued with a remaining external PTBD while 14 patients received an internal drainage but these had a temporary external drainage either at the stenting procedure or later (fig 1). According to the X-ray findings the biliary obstruction was extrahepatic in 16 patients (12.7 %), intrahepatic in 59 patients (46.8 %), and combined extra- and intrahepatic in 60 patients (47.6 %). It could not be classified in 5 patients (4.0 %) (Table1).

Jaundice was the initial symptom of the malignant disease in 62 patients (44 %). The median value of bilirubin in plasma before PTBD was 237 umol/L (range 31-634). Within the first week after PTBD the bilirubin level decreased to 180 umol/L (range 17-545) and fourteen days after PTBD it was further decreased to 112 umol/L (range 16-443). After that there was only a small decrease with a median value of 103 umol/L. The majority of the patients decreased their bilirubin value in plasma but only 35 patients (25 %) reached a level below 52 mmol/L (double upper reference value) (fig 2). Twelve of them received neoadjuvant chemotherapy, and four patients also received postoperative chemotherapy. Two patients went into remission and the others had a median survival of 9 months, which was three months more than the total patient material (n=126). Some 100 patients had a bilirubin value higher than 52 mmol/L after PTBD (fig 2).

Pruritus occurred in 34 out of the 126 patients (27 %) before the PTBD but the median bilirubin value did not differ between them (279 mmol/L) and the 92 patients without pruritus (236 mmol/L). After PTBD pruritus was relieved in 19 patients (56 %). The bilirubin value was not correlated to pruritus or to survival.
Some 269 adverse events (AE/complications) were documented. Most common were pain demanding increased dose of opioids, local discomfort, and cholangitis/septicemia, (table 2). AE/complications associated with increased demand of opioid treatment were documented in 67 of 126 patients (53.2 %) and 12 patients (9.5 %) were treated with increased dose of opioids without any documented adverse event. Local discomfort was documented in 21 patients. If patients with local discomfort or increased doses of opioids were excluded 36.5 % of the patients developed an AE/complication. No adverse event was documented in 44 patients (34.9 %). Each of these patients had 2.1 AE/complications (mean value). Early mortality after PTBD was high and within 14 days 20 patients (16 %) had died due to the malignant disease. The survival is shown in figure 3 also showing that after 3 months 50 % had died.

Antibiotic prophylaxis was given to 69 patients of whom 32 % (n=22) developed some infectious complication (cholangitis, septicemia, wound infection), which is significantly lower than in patients without prophylaxis (n=71) where the corresponding figure was 51 % (p=0.02). The 2-week mortality did not differ (16% vs 15 %).

In 90 % of the patients there was no documented information in the case records about expected possible positive and negative effects of PTBD. **Discussion**

It has previously been reported that biliary drainage may improve immune function, improve nutritional status, and reduce the risk of infection in patients with biliary obstruction (2, 9, 10). It has, however, been shown in animal experiments that endotoxemia often persists after external biliary drainage. In a recent systematic review on palliation of advanced malignant hilar obstruction endoscopic drainage was compared with PTBD. It was concluded that PTBD
was associated with higher rates of successful biliary drainage and lower rates of cholangitis. Endoscopic drainage had lower rates of bleeding complications but overall there was no difference in adverse events (11). However, there are several publications reporting that endoscopic approach is the optimal method, particularly in distal obstruction (8, 11-13).

Our and other studies report a significant decrease in plasma bilirubin during the first week after PTBD (5, 14, 15). Pruritus is often out of proportion to the serum bilirubin level and its pathogenesis is poorly understood (13). The intensity of pruritus was decreased in half of our patients after PTBD but the correlation between pruritus and the bilirubin level in plasma seems to be weak. We agree with other authors that jaundice should not by itself be an indication for palliative PTBD except when the aim is to prepare the patient for chemotherapy, as the catheters not seldom require maintenance and adjustments to lifestyle (3, 11). On the other hand when the indication for drainage is relief of pruritus, drainage of even one segment of the liver may reduce the symptoms (3).

Some kind of adverse event after external PTBD was common and early mortality was high in our patient group with advanced malignant disease as has been reported by others (10, 14-16). In most other reports pain associated with local discomfort or increased demand of opioid treatment has not been included among complications or adverse events (16-20). However, a biliary drainage can cause significant pain (5, 11, 21). When this group was excluded in our study the complication rate was 34 %, which is in agreement with other reports (16-17). In a large study comprising both patients with benign disease and patients with malignant disease receiving external drainage or stent there were complications associated with the PTBD in 10 %. However, only bleeding, infection, and bile leak were included. A score based on a multivariate analysis of independent predictors for those complications was suggested (low
albumin level, bilirubin higher than 300 mmol/L, high WBC, low Hemoglobin, high C-reactive protein, and proceeding to stent) (20).

Cholestasis is associated with decreased effectiveness of clearance of bacteria and increased susceptibility to systemic infection (22). Cholangitis usually occurs after manipulation of the biliary tree with concomitant direct or enteric contamination (3). It has been reported that about half of the patients with biliary obstruction have positive bile cultures and biliary infection is a major risk factor after PTBD (23-24). Broad-spectrum antibiotic prophylaxis should therefore be recommended to all patients undergoing PTBD (13, 21, 23, 25). In our study, unfortunately only half of the patients received antibiotic prophylaxis and once more it was shown that patients with antibiotic prophylaxis had a significantly lower risk of getting infectious complications compared with those without antibiotic prophylaxis.

PTBD is most successful in patients with obstruction of the bile duct below the insertion of the cystic duct. On the other hand endoscopic treatment with metallic stents is favored in these cases because they offer complete drainage without the inconvenience of an external catheter. Previous attempts with endoscopic drainage of the biliary ducts had been done in some of our patients with varying location of the obstruction before the PTBD was performed. According to the high risk of adverse events PTBD should not automatically be a second line treatment until endoscopic treatment with rendezvous technique has been attempted (26-29). Today PTBD still has a role in high duct obstruction (Bismuth type III-IV) (6, 9, 11, 16). A recent study compared percutaneous transhepatic biliary stenting (PTBS) with endoscopic stenting in advanced malignancy (30). There was no significant difference in effectiveness of biliary drainage or survival time and the PTBS group had lower costs. The
early complication rate was lower in the PTBS group and the rate of late complications did not differ.

Hopefully more than the documented 10 % of the patients in our study received information of what could be expected after PTBD. Such documentation should include a careful description of the indication for PTBD and which palliation can be expected. Risks for inadequate effect of PTBD on jaundice, pruritus, and for various adverse events, as pain, bleeding, infectious complications, leakage, and also death should be discussed with the palliative patient.
References


Figure legends

Fig 1. Flow chart showing the number of patients undergoing percutaneous transhepatic cholangiography (PTC) from June 210-June 2013, and how 126 patients with permanent external drainage (PTBD) and 14 patients with temporary external drainage and later internal drainage became included in the study.

Fig 2. Bilirubin in plasma before PTBD (left column) and after PTBD (right column). Grey colour depicts number of patients with a bilirubin value of ≥52 umol/L and black colour a value of <52 umol/L. Three patients are missing in the bar showing bilirubin after PTBD.

Fig 3. Survival in 140 patients with biliary drainage due to advanced malignant disease.
Table 1. Characteristics of 140 patients with malignant disease causing biliary obstruction with a value of bilirubin in plasma of ≥26 umol/L.

<table>
<thead>
<tr>
<th>Gender, n</th>
<th>Male</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median age (range)</th>
<th>70 (33-91)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ASA classification, n (%)</th>
<th>I</th>
<th>10 (7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
<td>49 (35%)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>44 (32%)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>7 (5%)</td>
</tr>
<tr>
<td></td>
<td>Not specified</td>
<td>30 (21%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer diagnosis, n (%)</th>
<th>Previously unknown</th>
<th>62 (44%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gallbladder/Biliary duct</td>
<td>26 (19%)</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>19 (14%)</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
<td>13 (9%)</td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>7 (5%)</td>
</tr>
<tr>
<td></td>
<td>Other origin</td>
<td>13 (9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of biliary obstruction assessed radiologically, n (%)</th>
<th>Intrahepatic</th>
<th>59 (42%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extrahepatic</td>
<td>16 (11%)</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>60 (43%)</td>
</tr>
<tr>
<td></td>
<td>Not specified</td>
<td>5 (4%)</td>
</tr>
</tbody>
</table>
Table 2. Distribution of 269 adverse events/complications within 14 days after external PTBD. Percentage of a certain adverse event is shown within brackets. More than one adverse event occurred often in the same patient (mean value 2.1).

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in opioids because of pain</td>
<td>82</td>
<td>30</td>
</tr>
<tr>
<td>Infection (septicemia, cholangitis, wound infection)</td>
<td>57</td>
<td>21</td>
</tr>
<tr>
<td>Local discomfort at the abdominal wall</td>
<td>50</td>
<td>19</td>
</tr>
<tr>
<td>Leakage</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>Hemorrhage demanding transfusions</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Fluid overload treated with diuretic drugs</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Other complications</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 3. Number of patients (n=67) with some adverse event/complication after PTBD

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholangitis/ Septicemia</td>
<td>31</td>
</tr>
<tr>
<td>Local discomfort at the abdominal wall</td>
<td>21</td>
</tr>
<tr>
<td>Leakage</td>
<td>3</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3</td>
</tr>
<tr>
<td>Dislocated PTBD</td>
<td>2</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1</td>
</tr>
<tr>
<td>Other AE/complications</td>
<td>6</td>
</tr>
</tbody>
</table>
Fig 1. Flow chart showing the number of patients undergoing percutaneous transhepatic cholangiography (PTC) from June 210-June 2013, and how 126 patients with external drainage (PTD) became included in the study.

PTC procedures 516

- Controls, adjustments, replacements of existing PTBD 301

Novel PTC 215

- Bil <26 umol/L (malignant disease, benign disease, part of extensive liver surgery) 75

Bil ≥26 umol/L 140

- Internal stent 14

PTBD 126
Fig 2

The bar chart shows the number of patients with bilirubin levels before and after intervention.

- Before intervention:
  - Bilirubin ≥ 52: 133 patients
  - Bilirubin < 52: 7 patients

- After intervention:
  - Bilirubin ≥ 52: 100 patients
  - Bilirubin < 52: 37 patients
Fig 3

Survival

Days after PTBD