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Pre-operative biliary drainage for obstructive jaundice

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Abstract

Background—Patients with obstructive jaundice have various pathophysiological changes that affect the liver, kidney, heart, and the immune system. There is considerable controversy as to whether temporary relief of biliary obstruction prior to major definitive surgery (pre-operative biliary drainage) is of any benefit to the patient.

Objectives—To assess the benefits and harms of pre-operative biliary drainage versus no pre-operative biliary drainage (direct surgery) in patients with obstructive jaundice (irrespective of a benign or malignant cause).

Search methods—We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Clinical Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, and Science Citation Index Expanded until February 2012.

Selection criteria—We included all randomised clinical trials comparing biliary drainage followed by surgery versus direct surgery, performed for obstructive jaundice, irrespective of the sample size, language, and publication status.

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CONTRIBUTIONS OF AUTHORS

Y Fang: update of the present review; searching for trials, quality assessment of trials, data extraction, data analyses, contributed to the results and discussion, and developed the draft of the review.

KS Gurusamy: lead author of the protocol of the present review; searching for trials, risk of bias assessment of trials, data extraction, data analyses, revised the review and wrote the discussion for this version of the review.

Q Wang: data analysis, contributed to discussion, and modified the draft of the previous version of the review to reach Cochrane standards.

BR Davidson: critically commented on the review and contributed to discussion.

L He: searching for trials, contributed to discussion.

X Xie: searching for trials, risk of bias assessment of the trials.

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DECLARATIONS OF INTEREST The authors who have been involved in this review have done so without any known conflicts of interest. They are not involved in any of the primary trials included in this systematic review.

Data collection and analysis—Two authors independently assessed trials for inclusion and extracted data. We calculated the risk ratio (RR), rate ratio (RaR), or mean difference (MD) with 95% confidence intervals (CI) based on the available patient analyses. We assessed the risk of bias (systematic overestimation of benefit or systematic underestimation of harm) with components of the Cochrane risk of bias tool. We assessed the risk of play of chance (random errors) with trial sequential analysis.

Main results—We included six trials with 520 patients comparing pre-operative biliary drainage (265 patients) versus no pre-operative biliary drainage (255 patients). Four trials used percutaneous transhepatic biliary drainage and two trials used endoscopic sphincterotomy and stenting as the method of pre-operative biliary drainage. The risk of bias was high in all trials. The proportion of patients with malignant obstruction varied between 60% and 100%. There was no significant difference in mortality (40/265, weighted proportion 14.9%) in the pre-operative biliary drainage group versus the direct surgery group (34/255, 13.3%) (RR 1.12; 95% CI 0.73 to 1.71; $P = 0.60$). The overall serious morbidity was higher in the pre-operative biliary drainage group (60 per 100 patients in the pre-operative biliary drainage group versus 26 per 100 patients in the direct surgery group) (RaR 1.66; 95% CI 1.28 to 2.16; $P = 0.0002$). The proportion of patients who developed serious morbidity was significantly higher in the pre-operative biliary drainage group (75/102, 73.5%) in the pre-operative biliary drainage group versus the direct surgery group (37/94, 37.4%) ($P < 0.001$). Quality of life was not reported in any of the trials. There was no significant difference in the length of hospital stay (2 trials, 271 patients; MD 4.87 days; 95% CI -1.28 to 11.02 ; $P = 0.12$) between the two groups. Trial sequential analysis showed that for mortality only a small proportion of the required information size had been obtained. There seemed to be no significant differences in the subgroup of trials assessing percutaneous compared to endoscopic drainage.

Authors' conclusions—There is currently not sufficient evidence to support or refute routine pre-operative biliary drainage for patients with obstructive jaundice. Pre-operative biliary drainage may increase the rate of serious adverse events. So, the safety of routine pre-operative biliary drainage has not been established. Pre-operative biliary drainage should not be used in patients undergoing surgery for obstructive jaundice outside randomised clinical trials.

Medical Subject Headings (MeSH)

Drainage [adverse effects; *methods]; Jaundice, Obstructive [mortality; surgery; *therapy]; Postoperative Complications; Randomized Controlled Trials as Topic; Stents

MeSH check words

Humans

BACKGROUND

Description of the condition

Obstructive jaundice is the term used for the increased serum bilirubin levels as result of obstruction to the flow of bile due to blockage in the large bile ducts. The clinical symptoms and signs of obstructive jaundice include yellow discolouration of skin and conjunctiva, dark

urine, pale stools, and pruritus. The main causes of obstructive jaundice include benign common bile duct stones or benign biliary stricture (secondary to common bile duct stones or a complication of cholecystectomy) and malignancy due to periampullary cancers (Bjornsson 2008). Periampullary cancer is the term used for cancers that form near the ampulla of Vater (NCI 2012) and includes cancer of the head and neck of the pancreas, cancer of the distal end of the bile duct, cancer of the ampulla of Vater, and cancer of the second part of the duodenum. Surgical resection is generally considered the only curative treatment for malignant obstructive jaundice. Approximately 20% of periampullary cancers presenting to surgeons are resectable (Michelassi 1989; Engelken 2003; Smith 2008).

Description of the intervention

Obstructive jaundice affects various organs and physiologic mechanisms in the body and can result in kidney failure (Wadei 2006), cardiac dysfunction (Wadei 2006), liver injury (Pauli-Magnus 2005), haemostatic abnormalities (Papadopoulos 2007), and altered body immunity (Nehez 2002). Restoration of biliary flow prior to operation (pre-operative biliary drainage) can be performed by percutaneous transhepatic biliary drainage under radiologic guidance or endoscopic sphincterotomy and placement of a stent across the obstruction of the biliary tract (Pisters 2001). Patients presenting with cholangitis may require pre-operative biliary drainage to allow their condition to improve sufficiently to allow surgery. However, many physicians routinely perform pre-operative drainage in patients with malignant obstructive jaundice (Kawasaki 2003) with the intention of relieving the biliary obstruction and reversing the pathophysiological changes caused by obstructive jaundice.

How the intervention might work

Pre-operative drainage relieves the obstruction and may reverse the pathophysiological dysfunction caused by obstructive jaundice. As a result, the patient-relevant outcomes may improve.

Why this review is important

A previous meta-analysis showed that pre-operative biliary drainage in patients with malignant obstructive jaundice carries no benefit and should not be performed routinely (Sewnath 2002). In our previous Cochrane systematic review (Wang 2008), we concluded that there is no evidence to support or refute pre-operative biliary drainage for patients with obstructive jaundice. However, the trials included in these two reviews were old and the applicability of the two reviews in modern surgical practice can be questioned. In this updated version, which includes a new trial (van der Gaag 2010), we have revised the methods in line with the revision of the methods in Cochrane reviews (Higgins 2011), and reanalysed and revised our interpretation of the data.

OBJECTIVES

To assess the benefits and harms of pre-operative biliary drainage in patients with obstructive jaundice (irrespective of a benign or malignant cause).

METHODS

Criteria for considering studies for this review

Types of studies—We included only randomised clinical trials irrespective of language, blinding, or publication status. Quasi-randomised studies (in which the method used to assign participants to a treatment group was not strictly random, for example, date of birth, hospital record number, and alternation) and other study designs were not included in this review due to the risk of bias.

Types of participants—Participants were patients with obstructive jaundice, irrespective of a benign or malignant cause, who were about to undergo surgery.

Types of interventions—We included trials comparing pre-operative biliary drainage with no pre-operative biliary drainage (direct surgery). Co-interventions were allowed provided that they were used equally in both groups.

Types of outcome measures

Primary outcomes:

1. Survival:
 - i. hazard ratio (at maximal follow-up);
 - ii. mortality within three months (procedure or operative mortality).
2. Serious morbidity (serious complications, as classified by the authors, or grade 3 or grade 4 Clavien-Dindo classification (Dindo 2004; Clavien 2009)). This approximately corresponded to the serious adverse events of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice (ICHGCP) (ICH-GCP 1997).
 - i. Surgery-related morbidity.
 - ii. Procedure-related morbidity.
3. Quality of life.

Secondary outcomes:

1. Total length of hospital stay.
2. Costs.

Search methods for identification of studies

Electronic searches—We searched the Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2012), Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, and Science Citation Index Expanded (Royle 2003) until February 2012. We have given the search strategies in Appendix 1 with the time spans for the searches.

Searching other resources—We also searched the references of the identified trials and the metaRegister of Controlled Trials, which includes the ISRCTN and NIH ClinicalTrials.gov trial registers, to identify further relevant trials.

Data collection and analysis

Selection of studies—CHW, KSG, and YF independently identified the trials for inclusion. We listed the excluded studies with the reasons for the exclusion.

Data extraction and management—KSG and YF independently extracted the following data.

1. Year and language of publication.
2. Country.
3. Year of study.
4. Inclusion and exclusion criteria.
5. Details of intervention and control.
6. Co-interventions.
7. Outcomes (listed above).
8. Risk of bias (described below).

Assessment of risk of bias in included studies: We independently assessed the risk of bias in the trials without masking the trial names. We followed the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2012). Due to the risk of biased overestimation of beneficial intervention effects in randomised trials with high risk of bias (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008), we assessed the following domains of risk of bias in the trials.

Sequence generation:

- Low risk of bias: the method used is either adequate (eg, computer generated random numbers, table of random numbers) or unlikely to introduce confounding.
- Uncertain risk of bias: there is insufficient information to assess whether the method used is likely to introduce confounding.
- High risk of bias: the method used (eg, quasi-randomised studies) is inappropriate and likely to introduce confounding.

Allocation concealment:

- Low risk of bias: the method used (eg, central allocation) is unlikely to introduce bias in determining the final observed effect.
- Uncertain risk of bias: there is insufficient information to assess whether the method used is likely to introduce bias for the estimate of effect.

- High risk of bias: the method used (eg, open random allocation schedule) is likely to introduce bias on the final observed effect estimate.

Blinding:

- Low risk of bias: the patients and outcome assessors were blinded and the method of blinding was described.
- Uncertain risk of bias: the patients and outcome assessors were blinded and the method of blinding was not described.
- High risk of bias: the patients or outcome assessors were not blinded.

Incomplete outcome data:

- Low risk of bias: the underlying reasons for missing data are unlikely to make treatment effects depart from plausible values, or proper methods have been employed to handle missing data.
- Uncertain risk of bias: there is insufficient information to assess whether the missing data mechanism in combination with the method used to handle missing data are likely to introduce bias for the estimate of effect.
- High risk of bias: the crude estimate of effects (eg, complete case estimate) will clearly be biased due to the underlying reasons for missing data and the methods used to handle missing data are unsatisfactory.

Selective outcome reporting:

- Low risk of bias: pre-defined or clinically relevant and reasonably expected outcomes (such as short-term mortality and serious adverse events either reported as number of patients with serious adverse events or total number of serious adverse events) are reported on.
- Uncertain risk of bias: not all pre-defined or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Vested interest bias:

- Low risk of bias: if the trial is conducted according to a publicly available protocol or if it is conducted by a party without any vested interests in the outcome of the trial.
- Uncertain risk of bias: if the trial protocol is not available and if it is not clear if the trial is conducted by a party with a vested interest in the outcome of the trial.

- High risk of bias: if the trial is not conducted according to a publicly available protocol, a protocol is not available, or the trial is conducted by a party with vested interests in the outcome of the trial.

We considered trials to have a low risk of bias if we assessed all the above domains as being at low risk of bias. In all other cases, the trials were considered to have a high risk of bias.

Measures of treatment effect: For dichotomous variables, we calculated the risk ratio (RR) with 95% confidence interval (CI). We also planned to report the risk difference if it was different from the RR since risk difference includes trials with zero events in both groups and allows meta-analysis. For continuous variables, we planned to calculate the mean difference (MD) with 95% CI for hospital stay; and the standardised mean difference (SMD) with 95% CI for variables such as quality of life. For serious adverse events, we calculated the rate ratio (RaR) with 95% CI. For time-to-event variables, we calculated the hazard ratio (HR) with 95% CI.

Unit of analysis issues: The unit of analysis was the aggregate data on patients with benign or malignant obstructive jaundice who were about to undergo surgery according to the group they were randomised to.

Dealing with missing data: We performed an intention-to-treat analysis (Newell 1992) whenever possible. We imputed data for binary outcomes using various scenarios, namely best-best analysis, worst-worst analysis, best-worst analysis, and worst-best analysis (Gurusamy 2009; Gluud 2012).

For continuous outcomes, we used available-case analysis. We imputed the standard deviation from P values according to the instructions given in the Cochrane Handbook for Systematic Reviews of Intervention (Higgins 2011) and used the median for the meta-analysis when the mean was not available. If it was not possible to calculate the standard deviation from the P value or the confidence intervals, we imputed the standard deviation as the highest standard deviation in the other trials included under that outcome, fully recognising that this form of imputation will decrease the weight of the trial for calculation of mean differences and bias the effect estimate to no effect in the case of standardised mean difference (Higgins 2011).

Assessment of heterogeneity: We examined the forest plot to visually assess heterogeneity. Overlapping of CIs was used to assess the heterogeneity visually. We explored heterogeneity by the χ^2 test with significance set at a P value of 0.10, and measured the quantity of heterogeneity by the I^2 statistic (Higgins 2002).

Assessment of reporting biases: We planned to use a funnel plot to explore bias in the presence of at least 10 trials (Egger 1997; Macaskill 2001). We planned to use asymmetry in the funnel plot of trial size against treatment effect to assess this bias. We also planned to use the linear regression approach described by Egger et al (Egger 1997) to determine the funnel plot asymmetry.

Data synthesis: We performed the meta-analyses according to the recommendations of The Cochrane Collaboration (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2012) using the software package Review Manager 5 (RevMan 2011). We use a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987). In the case of a discrepancy between the two models we have reported both results; otherwise we have reported only the results from the fixed-effect model.

Subgroup analysis and investigation of heterogeneity: We planned to perform the following subgroup analyses.

- Trials with low risk of bias compared with trials of unclear or high risk of bias.
- Method of pre-operative biliary drainage (percutaneous transhepatic biliary drainage compared to endoscopic method).
- Trials with equal to or more than 95% of patients having malignant jaundice compared to trials with less than 95% with malignant jaundice.

We were unable to perform the subgroup analysis of trials at low risk of bias versus those trials with a high risk of bias since there were no trials at low risk of bias. We were able to perform the other two subgroup analyses. We performed the χ^2 test for subgroup differences, setting a P value of 0.05 to identify any differences.

Sensitivity analysis: We planned to perform a sensitivity analysis by imputing the outcomes for binary outcomes under different scenarios, namely best-best analysis, worst-worst analysis, best-worst analysis, and worst-best analysis (Gurusamy 2009; Gluud 2012), for any significant binary outcome. We also performed a sensitivity analysis by excluding the trials in which medians or standard deviations were imputed for the continuous outcomes. Both these sensitivity analyses were planned. We also performed post hoc sensitivity analyses by excluding Lai 1994 (the severity of complications could not be assessed), Pitt 1985 (as this trial included a significant proportion of proximal obstructions), and van der Gaag 2010 (as routine antibiotic prophylaxis was not used for distal obstructions). We also performed another post hoc sensitivity analysis including all bile leaks irrespective of the way they were treated, except those leaks which clearly resolved spontaneously. Bile leaks are post-operative complications. Some resolve spontaneously without any prolongation of hospital stay and hence will be assessed as mild adverse events. Other bile leaks need radiological or endoscopic interventions and hence will be classified as serious adverse events. If the trial authors did not report the way the bile leaks were treated then it is not possible to determine their severity. So, we performed two analyses, one excluding the bile leaks which resolved spontaneously and those for which the treatment was not reported, and another including the bile leaks for which the treatment was not reported but excluding the bile leaks which clearly resolved spontaneously.

Trial sequential analysis: We applied trial sequential analysis (CTU 2011; Thorlund 2011) using a required information size calculated from an alpha error of 0.05, a beta error of 0.20, a control event proportion obtained from the results, and a relative risk reduction of 20% for mortality to determine whether more trials are necessary on this topic (if the alpha spending boundary or the futility zone is crossed, then more trials are unnecessary) (Brok 2008;

Wetterslev 2008; Brok 2009; Thorlund 2009, Wetterslev 2009; Thorlund 2010). We did not perform a trial sequential analysis for serious morbidity since only one trial reported the proportion of patients with serious morbidity and since the methods for trial sequential analysis of RaR have not been established.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search—A total of 4260 references were identified from medical journal databases. One additional reference was identified through the reference search. No additional trial was identified through the meta-register of Current Controlled Trials. The flow of references is shown in Figure 1 (PRISMA flow diagram) (Moher 2009). In total, 14 references described six completed randomised clinical trials that fulfilled the inclusion criteria (Hatfield 1982; McPherson 1984; Pitt 1985; Lai 1994; Wig 1999; van der Gaag 2010). A total of 520 patients randomised to pre-operative biliary drainage (265 patients) versus no pre-operative biliary drainage (255 patients) were included in the six trials. This included one new trial (van der Gaag 2010), which increased the number of patients included in the meta-analysis from 324 patients in the previous review to 520 patients in the updated review, that is, an increase of approximately 60%.

Included studies—Four trials used percutaneous transhepatic biliary drainage as the method of drainage (Hatfield 1982; McPherson 1984; Pitt 1985; Wig 1999). Two trials used endoscopic sphincterotomy as the method of drainage (Lai 1994; van der Gaag 2010). The mean duration of drainage in the trials varied between one and six weeks (Hatfield 1982; McPherson 1984; Pitt 1985; Lai 1994; Wig 1999; van der Gaag 2010). One trial did not routinely administer antibiotic prophylaxis for drainage in cases of distal bile duct obstruction, but peri-operative antibiotics were administered (van der Gaag 2010). Antibiotics were used routinely for pre-operative biliary drainage and for surgery in the remaining trials.

Two trials included only patients with malignant obstructive jaundice (McPherson 1984; Lai 1994). The proportion of patients with malignant obstructive jaundice in the other trials was 95% (Hatfield 1982), 92% (van der Gaag 2010), 77% (Pitt 1985), and 60% (Wig 1999). One trial (van der Gaag 2010) included patients with bilirubin levels between 40 $\mu\text{mol/l}$ and 250 $\mu\text{mol/l}$. The remaining trials included patients with minimum bilirubin levels ranging between 100 $\mu\text{mol/l}$ and 172 $\mu\text{mol/l}$ (Hatfield 1982; McPherson 1984; Pitt 1985; Lai 1994; Wig 1999). One trial stated that only patients in an operable condition were included (Pitt 1985). Another trial stated that the patients were fit for major surgery (van der Gaag 2010). One trial stated that patients with ongoing cholangitis were excluded (van der Gaag 2010). The other trials did not state whether they excluded such patients. Most of the patients included in the trials were patients with distal common bile duct obstruction. Further details about the included trials are shown in the table 'Characteristics of included studies'.

Excluded studies—One study was excluded because the randomisation was by hospital file numbers, that is, this was a quasi-randomised study. This is shown in the table ‘Characteristics of excluded studies’.

Risk of bias in included studies

The risk of bias is summarised in the ‘Risk of bias’ graph (Figure 2) and ‘Risk of bias’ summary (Figure 3). All the trials were at high risk of bias.

Effects of interventions

See: Summary of findings for the main comparison Pre-operative biliary drainage versus direct surgery for obstructive jaundice

Mortality—There was no significant difference in mortality between the two intervention groups (RR 1.12; 95% CI 0.73 to 1.71; $P = 0.60$) (Analysis 1.1). The mortality was 15.1% (40/265) in the pre-operative biliary drainage group versus 13.3% (34/255) in the direct surgery group. There was no change in the results by following a random-effects model. Heterogeneity was not statistically significant ($I^2 = 0\%$; $P = 0.67$). The tests for subgroup differences were not statistically significant for subgroup analyses according to method of pre-operative biliary drainage (Analysis 2.1) or proportion of patients with malignant jaundice (equal to or more than 95% compared to less than 95%) (Analysis 3.1). Long-term survival was reported in only one trial. There was no significant difference in the long-term survival between the two groups in patients who underwent successful pancreatoduodenectomy for cancer in the only trial that reported this outcome (HR 0.90; 95% CI 0.65 to 1.24) (van der Gaag 2010) (Analysis 1.2). Only 520 patients of the estimated 11,130 patients required to rule out differences in mortality have been recruited so far.

Serious morbidity (serious adverse events)—There was a significantly higher occurrence of serious morbidity in the pre-operative biliary drainage group than in the direct surgery group (RaR 1.66; 95% CI 1.28 to 2.16; $P = 0.0002$) (Analysis 1.3). There was no change in results by following a random-effects model. Heterogeneity was not statistically significant ($I^2 = 44\%$; $P = 0.11$). The tests for subgroup differences were not statistically significant for the subgroup analyses (Analysis 2.2) (Analysis 3.2). We performed post hoc sensitivity analyses by excluding the trials by Lai et al (severity of complications could not be assessed) (Lai 1994), Pitt et al (this trial included a significant proportion of proximal obstructions) (Pitt 1985), and van der Gaag et al (van der Gaag 2010) (routine antibiotic prophylaxis was not used for distal obstructions); and by including bile leaks irrespective of the management. There was no change in the results with any of these sensitivity analyses (Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4).

The proportion of patients with serious morbidity was reported in only one trial (van der Gaag 2010). The proportion of patients who developed serious morbidity was significantly higher in the group of patients who had pre-operative biliary drainage than in the direct surgery group (75/102 (73.5%) in the pre-operative biliary drainage group versus 37/94 (39.3%) with direct surgery; Fisher’s exact test $P < 0.001$) (Analysis 1.4).

Quality of life—None of the trials reported this outcome.

Hospital stay—Meta-analysis of two trials (Pitt 1985; van der Gaag 2010) showed a significantly longer hospital stay in the pre-operative biliary drainage group using the fixed-effect model (MD 4.26 days; 95% CI 0.92 to 7.61; $P = 0.01$) (Analysis 1.4) but not with the random-effects model (MD 4.87 days; 95% CI -1.28 to 11.02; $P = 0.12$) (Analysis 1.5). Heterogeneity was statistically significant ($I^2 = 68\%$; $P = 0.08$). We did not perform a subgroup analysis because of the presence of only two trials for this outcome. Sensitivity analysis excluding the trial by van der Gaag et al (van der Gaag 2010), in which the mean and standard deviation was imputed from the median and P value, resulted in the inclusion of only one trial (Pitt 1985) that showed a significantly longer hospital stay in the pre-operative biliary drainage group than in the direct surgery group.

Cost—None of the trials reported this outcome.

Reporting bias—We did not explore reporting bias because of the presence of fewer than 10 trials.

Trial sequential analysis—The alpha-spending boundaries and the boundaries of futility were not reached (Figure 4).

DISCUSSION

Summary of main results

Our review showed that combining pre-operative biliary drainage with surgery compared with direct surgery increased the proportion of serious adverse events without any apparent significant advantages. The overall mortality in patients with obstructive jaundice undergoing surgery was approximately 15.1% in the pre-operative biliary drainage group and 13.3% in the control group (no statistically significant difference). One of the factors in this finding that we explored was whether this represents the current situation since many of the trials were old. So, we calculated the mortality excluding the trial by van der Gaag et al (van der Gaag 2010), which recruited patients between November 2003 and June 2008 and contributed nearly 40% of the patients in the review. In this trial, the mortality of patients in the pre-operative biliary drainage group was 14.7% compared with 12.8% in the no pre-operative biliary drainage group (no statistically significant difference). The overall mortality in the other trials (that is, excluding the trial by van der Gaag et al (van der Gaag 2010)) was similar (15.3% in the pre-operative biliary drainage group and 13.7% in the no pre-operative biliary drainage group) demonstrating no significant reduction in the mortality associated with major surgeries in patients with obstructive jaundice over time. This is in contrast to the generally quoted mortality of 2% to 4% for pancreatico-duodenectomy (Winter 2006; Diener 2011) and may reflect the severity of the jaundice or the severity of cancer in the patients included in the trials.

There was no significant difference between the two intervention groups with regards to mortality in the present review. The main question is whether this is a lack of effect or lack of evidence of an effect. We used trial sequential analysis (Wetterslev 2008; Wetterslev

2009) with an alpha error of 0.05, beta error of 0.20, control event proportion of 13%, and a relative risk reduction of 20% to identify whether the region of futility was reached. This analysis revealed that the region of futility was not yet reached, and so we cannot rule out any difference in the mortality between pre-operative biliary drainage and direct surgery. In addition, we utilised the definition of imprecision of results used by the GRADE handbook for grading quality of evidence and strength of recommendation (Schünemann 2009)(which is currently recommended by The Cochrane Collaboration for grading the level of evidence, <http://ims.cochrane.org/revman/other-resources/gradepr>). The total number of events in this review was less than 400 and the CI for mortality (RR 1.12; 95% CI 0.73 to 1.71) overlaps no effect (that is, RR of 1) and appreciable benefit or harm (25% increase, that is, RR of 1.25; and 25% reduction, that is, RR of 0.75). This supports the results of the trial sequential analysis that one cannot rule out a difference in the mortality between pre-operative biliary drainage and direct surgery. The long-term survival was reported in only one of the trials. There was no significant difference between the two groups. Again, the CI was wide for this outcome. So, we are unable to rule out any difference in the long-term survival between pre-operative biliary drainage and direct surgery.

The overall severe morbidity was higher in the pre-operative biliary drainage group than the direct surgery group. This difference is consistent with different statistical methods used and various sensitivity analyses. There was heterogeneity in the outcome, mainly because of the magnitude of the effect rather than the direction of the effect; that is, the number of serious adverse event was higher in the pre-operative biliary drainage group. The proportion of patients with serious adverse events was also higher in the pre-operative biliary drainage group than the direct surgery group, although this information is only from one recent trial (van der Gaag 2010). The definitions used for serious adverse events were those used by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and are used by regulatory authorities such as the Food and Drug Administration (FDA), MDA, and Japan Society of Quality Assurance (JSQA) in US, Europe, and Japan, respectively (ICH-GCP 1997) in determining the adverse events related to a pharmacological intervention. While it is not mandatory to report radiological, endoscopic, and surgical interventions using these definitions, we have used these definitions in the absence of any other universal definitions for complications. Serious adverse events of the ICH-GCP classification roughly correspond to class III or class IV in the Clavien-Dindo classification (Dindo 2004; Clavien 2009), the only validated classification system in assessing surgical interventions. Inevitably, some information will be lost by using such classifications which pool complications together. However, unless such an approach is followed, it is difficult to power trials related to surgery using any meaningful outcomes to the patients. We acknowledge that some complications are temporarily worse than others in terms of treatment required to resolve complications, prolongation of hospital stay, and the cost implications. However, the use of generic definitions for complications enables comparison of treatment across different disciplines of medicine. Until further validated definitions of serious adverse events become available, it is reasonable to use the definitions that are currently used by regulatory authorities in US, Europe, and Japan to assess pharmacological interventions on non-pharmacological interventions.

None of the trials reported quality of life. Adequate decompression of the biliary obstruction may improve the quality of life by reducing the symptoms of biliary obstruction such as itching. On the other hand, it may produce anxiety by delaying surgery while waiting for resolution of jaundice and because of the complications related to the pre-operative biliary drainage procedure. From a patient's perspective, long-term survival and quality of life (which takes any permanent disability or morbidity into account) are the important determinants that should guide the healthcare provider about the use of the procedure. However, in the absence of differences in such long-term outcomes, short-term outcomes such as morbidity and hospital stay may be quite important. From a health funder perspective, cost per quality adjusted life year (QALY), which takes into account long-term survival and quality of life along with short-term outcomes such as morbidity (and the cost for management of the morbidity) and hospital stay, are important determinants to fund or not to fund the treatment. Hospital stay in the pre-operative biliary drainage group will include the hospital stay to perform the drainage, repeat the procedure if the drainage is not adequate, and treat any complications resulting from pre-operative biliary drainage along with the post-operative hospital stay. Considering that the morbidity is higher in the pre-operative biliary drainage group without any beneficial effects funding for pre-operative biliary drainage seems inappropriate.

One of the important questions that needs to be answered was whether pre-operative biliary drainage was performed appropriately. Pre-operative biliary drainage is aimed at restoring the flow of bile in patients with obstructive jaundice, thereby reversing the pathophysiological changes due to obstructive jaundice. The criteria used to assess success of pre-operative biliary drainage and the duration of pre-operative biliary drainage varied between the trials. A short drainage time may not be enough to demonstrate benefit, but a long drainage time may increase the risk of pre-operative biliary drainage-related complications and allow cancer progression. There is very little information available about the duration of the drainage period required to reverse the pathophysiological changes associated with obstructive jaundice, and so the optimal duration of drainage is not clear. There is also considerable controversy about the method of drainage and the type of stent used (Moss 2007; Kloek 2010).

Overall completeness and applicability of evidence

This evidence is applicable to patients with obstructive jaundice who are fit for direct surgery, that is, do not have sepsis that precludes a major operation and those who undergo neoadjuvant therapy where an alternative treatment such as chemotherapy is carried out before definitive surgery is performed (Cheng 2006).

Quality of the evidence

As regards the quality of evidence, we assessed this under the headings described by the GRADE handbook for grading quality of evidence and the strength of the recommendation (Schünemann 2009). This included the risk of bias in the trials and consistency and directness of evidence apart from the precision of the results, which was discussed earlier. As regards the risk of bias, all the trials were at a high risk of bias. Allocation was unclear in most of the trials. Blinding of outcome assessors was not performed in most of the trials.

Most of the trials had post-randomisation dropouts (Characteristics of included studies). From the information available from the trials regarding post-randomisation drop-outs, there is no specific mechanism of drop-out. Considering that the intervention was started pre-operatively and that no surgery was carried out in patients who did not meet the inclusion criteria or refused the surgery, it appears that post-randomisation dropouts are inevitable. While an available patient analysis may be appropriate when the drop-outs are not related to the intervention (Gurusamy 2009), strict intention-to-treat analysis has to be followed in this situation since some patients could become unresectable during pre-operative biliary drainage (while waiting for definitive surgery). Overall, the risk of bias is high and the true effect may be different from the effect obtained in this meta-analysis. As regards consistency, as discussed previously the effect of pre-operative biliary drainage on mortality appears to be consistent, while the magnitude of the effect on serious adverse events is not consistent across trials. As far as directness of evidence is concerned, there is not much concern about the directness of short-term mortality and morbidity. However, there is little information available related to quality of life and to long-term morbidity and mortality. However, in spite of all these deficiencies in the quality of evidence, this review seems to be the best evidence available on this topic.

Potential biases in the review process

We followed the *Cochrane Handbook for Systematic Reviews of Interventions* for this review (Higgins 2011). There were no language, publication status, or sample size restrictions. Thus, we minimised the bias due to the selection of only randomised clinical trials. We were unable to assess reporting bias because of the few trials identified. The intervention has been available for several years now, including the pre-mandatory trial registration era, so we cannot be sure whether there are any unreported or unidentified trials. However, one has to be pragmatic and accept that the results of such trials are unlikely to be available in the near future and we have assessed the information that is available.

Agreements and disagreements with other studies or reviews

Based on the above discussions, it appears that there is no strong evidence to recommend or refute pre-operative biliary drainage. So, should we allow individual clinicians to treat patients according to their preference? The answer is 'no', as this can result in fragmentation of care and can lead to suboptimal performance (Swensen 2010). It is necessary to standardise treatments and develop guidelines in order to improve health care (Swensen 2010). Adoption of routine pre-operative biliary drainage into clinical practice was not evidence-based. In spite of randomised trials repeatedly showing lack of evidence of any benefit of pre-operative biliary drainage, clinicians continue to use routine pre-operative biliary drainage (Kawasaki 2003). One can argue that our recommendation is based on randomised trials at high risk of bias. However, the argument for the routine use of pre-operative biliary drainage is based on even more flawed study designs. Furthermore, randomised trials with high risk of bias usually overestimate intervention benefits and underestimate the intervention harms of the experimental intervention, that is, pre-operative biliary drainage. As we have identified risks of significant harms in the included trials, our results suggest that the reality may be worse. One should not justify current mistakes based on past errors. Instead, it is reasonable to acknowledge past mistakes and avoid such

mistakes in the future. We acknowledge that new randomised clinical trials may show results which are different from the conclusions of our systematic review. There are no new randomised clinical trials registered in the metaRegister of Controlled Trials, which includes the major clinical trials registers. So, the evidence reviewed in our review is the best evidence available currently, which is likely to remain so for the next few years. One cannot base current practice on future speculative results but it ought to be based on the currently available information. Until new evidence with low risk of bias emerges, the present systematic review is the best available evidence on this topic.

In conclusion, pre-operative biliary drainage does not appear to be beneficial to the patients or healthcare funders in any way. It may increase serious adverse events and could add to the cost of the health care. We do not recommend routine use of pre-operative biliary drainage in patients with obstructive jaundice who are about to undergo surgery outside well-designed randomised clinical trials with low risk of systematic error and random error, and those trials that include long-term survival and quality of life as important outcomes. We recommend that routine pre-operative biliary drainage should not be funded. There may also be medico-legal implications of these findings, making physicians vulnerable to litigations in cases of complications related to routine pre-operative biliary drainage.

A previous meta-analysis showed that pre-operative biliary drainage with malignant obstructive jaundice carries no benefit and should not be performed routinely (Sewnath 2002). In our previous Cochrane review (Wang 2008), we concluded that there is no evidence to support or refute pre-operative biliary drainage for patients with obstructive jaundice. In this review we go one important step further and state that pre-operative biliary drainage should not be used routinely outside well designed randomised clinical trials.

AUTHORS' CONCLUSIONS

Implications for practice

We do not recommend routine use of pre-operative biliary drainage in patients with obstructive jaundice who are about to undergo surgery outside well designed randomised clinical trials.

Implications for research

Well designed randomised clinical trials with low risk of systematic error and random error and those that include long-term survival and quality of life as important outcomes may be necessary. Such trials ought to stratify patients according to the likely cause of obstruction as well as to report both short- and long-term outcomes such as quality of life, non-serious adverse events, serious adverse events, and mortality. The trials should also describe the results of the pre-operative drainage and any delay to surgery this may have caused. Reporting of such trials according to the CONSORT statement (<http://www.consort-statement.org/consort-statement/>) will enable transparent evaluation of the intervention.

Acknowledgments

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Disclaimer of the Department of Health: 'The views and opinions expressed in the review are those of the authors and do not necessarily reflect those of the National Institute for Health Research (NIHR), National Health Services (NHS), or the Department of Health.'

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Peer Reviewers: Ehab El-Hanafy, Egypt.

Contact Editors: Ronald L Korte, USA; Christian Gluud, Denmark.

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- None, Not specified.

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- National Institute for Health Research, UK.

Department of Health disclaimer: 'The views and opinions expressed in the review are those of the authors and do not necessarily reflect those of the NIHR,

NHS, or the Department of Health.'

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Hatfield 1982

Methods	Randomised clinical trial	
Participants	Country: South Africa. Sample size: 57. Post-randomisation drop-out(s): 10 (17.5%). Revised sample size: 47. Females: not stated. Mean age: 61.8 years. Number with malignancy: 52 /55 (95%) (characteristics of 55 patients were presented in the report). Inclusion criteria: 1. Patients with obstructive jaundice (ultrasound and ERCP proven). 2. Bilirubin more than 150 micromole/litre. Exclusion criteria: Patients with hepatocellular carcinoma.	
Interventions	The patients were randomised to the following groups. Group 1: pre-operative biliary drainage (n = 22). Further details: percutaneous transhepatic biliary drainage into external sealed bag system for 7 to 10 days (or longer if clinically indicated). Group 2: control (n = 25).	
Outcomes	The outcomes reported were mortality and overall morbidity.	
Notes	Reason for post-randomisation drop-out(s): hepatocellular carcinoma (1); cross-over (1); technical failures (3); operations unjustified (1); pre-operative deaths (4)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly allocated". Comment: the trial is described as randomised, but the method of sequence generation was not specified

Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomly allocated". Comment: the trial was described as randomised but the method used to conceal the allocation was not described
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: the trial was not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation drop-outs.
Selective reporting (reporting bias)	High risk	Comment: the severity of the complications was not reported.
Vested interest bias	Unclear risk	Quote: "Financial assistance was received from the South African Medical Research Council and the Staff Research Fund, University of Cape Town" Comment: says financial assistance was received but no mention that the entire study was funded by these research charities

Lai 1994

Methods	Randomised clinical trial	
Participants	Country: China. Sample size: 87. Post-randomisation drop-outs: 0 (0%). Revised sample size: 87. Females: 28 (32.2%). Mean age: 66.4 years. Number with malignancy: 87 (100%). Inclusion criteria: 1. Patients with malignant obstructive jaundice. 2. Serum bilirubin more than 100 micromol/litre.	
Interventions	The patients were randomised to the following groups. Group 1: pre-operative biliary drainage (n = 43). Further details: endoscopic drainage for at least 2 weeks. Group 2: control (n = 44).	
Outcomes	The outcomes reported were mortality and overall morbidity.	
Notes	Numbers of patients with complications rather than the number of complications were reported. The severity of the complications could not be determined	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomised". Comment: the trial is described as randomised, but the method of sequence generation was not specified
Allocation concealment (selection bias)	Unclear risk	Quote: "Eligible patients were randomised by drawing consecutively numbered envelopes that contained the assigned treatment". Comment: further details were not available.
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: the trial was not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no post-randomisation drop-outs.
Selective reporting (reporting bias)	High risk	Comment: the severity of the complications was not reported.
Vested interest bias	Unclear risk	Comment: the trial did not report the source of funding.

McPherson 1984

Methods	Randomised clinical trial	
Participants	Country: United Kingdom. Sample size: 70. Post-randomisation drop-out(s): 5 (7.1%). Revised sample size: 65. Females: not stated. Median age: 61.8 years. Number with malignancy: 65/65 (100%). Inclusion criteria: 1. Patients with malignant obstructive jaundice (confirmed by ultrasound and PTC). Exclusion criteria: 1. Patients with recurrent disease. 2. Patients with biliary obstruction due to secondary hilar deposits	
Interventions	The patients were randomised to the following groups. Group 1: pre-operative biliary drainage (n = 34). Further details: percutaneous transhepatic biliary drainage for 14 days or until bilirubin reached half its original value, into a closed drain system or using an antiseptic barrier. Group 2: control (n = 31).	
Outcomes	The outcomes reported were mortality and morbidity.	
Notes	Reason for post-randomisation drop-out(s): benign disease (4); metastatic deposit (1)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were matched first. Matched patients were then randomised to either drainage group or surgery group". "Toss of coin was used" Comment: the trial is described as randomised, but the method of sequence generation was not specified
Allocation concealment (selection bias)	Unclear risk	Quote: "Toss of coin used". Comment: the trial was described as randomised but the method used to conceal the allocation was not described
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: the trial was not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation drop-outs.
Selective reporting (reporting bias)	High risk	Comment: the severity of the complications was not reported.
Vested interest bias	Unclear risk	Quote: "This work was generously supported by a Cancer Research Campaign Grant". Comment: does not rule out additional support.

Pitt 1985

Methods	Randomised clinical trial	
Participants	Country: United States of America. Sample size: 79. Post-randomisation drop-out(s): 4 (5.1%). Revised sample size: 75. Females: 29 (36.7%). Mean age: 60.7 years. Number with malignancy: 58/75 (77.3%). Inclusion criteria: 1. Patients with obstructive jaundice. 2. Bilirubin greater than 171 micromoles/litre.	

	3. Patient was an operative candidate according to the attending physician's judgement. 4. Five or more previously described risk factors.	
Interventions	The patients were randomised to the following groups. Group 1: pre-operative biliary drainage (n = 37). Further details: percutaneous transhepatic biliary drainage into a closed drainage system until the bilirubin dropped below 171 micromoles/litre or the number of risk factors decreased to two. Group 2: control (n = 38).	
Outcomes	The outcomes reported were mortality, morbidity, and hospital stay	
Notes	Reason for post-randomisation drop-outs was not stated.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "From a list of random numbers at each institution, patients were randomised to receive percutaneous transhepatic drainage...." Comment: sequence generation was achieved using random number generation
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomly allocated". Comment: the trial was described as randomised but the method used to conceal the allocation was not described
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: the trial was not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation drop-outs.
Selective reporting (reporting bias)	High risk	Comment: the severity of the complications was not reported.
Vested interest bias	Unclear risk	Comment: the trial did not report the source of funding.

van der Gaag 2010

Methods	Randomised clinical trial
Participants	Country: Netherlands. Sample size: 202. Post-randomisation drop-out(s): 6(3%). Revised sample size: 196. Females: 77/196(39.3%). Mean age: 64.7 years. Number with malignancy: 181/196 (92.3%). Inclusion criteria: 1. Patients with obstructive jaundice due to cancer of the pancreatic head. 2. Bilirubin level of 40 to 250 μ mol per litre. 3. Age 18 to 85 years. 4. No evidence of distant metastasis or local vascular involvement. Exclusion criteria: 1. Patients with serious co-existing illness. 2. Contra-indications for major surgery. 3. Ongoing cholangitis. 4. Previous pre-operative biliary drainage. 5. Current recipient of neoadjuvant chemotherapy. 6. Presence of serious gastric outlet obstruction.
Interventions	The patients were randomised to the following groups. Group 1: pre-operative biliary drainage (n = 102). Further details: endoscopic drainage for 4 to 6 weeks. Group 2: control (n = 94).

Outcomes	The outcomes reported were mortality, morbidity, and hospital stay	
Notes	Total number of patients with complications rather than total number of complications were used. Reason for post-randomisation drop-out(s): did not meet inclusion criteria (4); withdrew consent (2) after allocation to the two groups	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization, which was stratified according to study center, was performed with a computer program at the coordinating trial center" Comment: sequence generation was achieved using computer random number generation
Allocation concealment (selection bias)	Low risk	Quote: "Randomization, which was stratified according to study center, was performed with a computer program at the coordinating trial center" Comment: allocation was controlled by a central and independent randomisation unit
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: an adjudication committee reviewed all events in a blinded fashion Comment: the trial was described as blinded, the assessor blinding was described
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation drop-outs after allocation of patients
Selective reporting (reporting bias)	Low risk	Comment: mortality and severe complications were reported.
Vested interest bias	High risk	Quote: "Dr. Bruno reports receiving lecture fees from Boston Scientific; and Dr. Greve, consulting fees from GI Dynamics and lecture fees from Covidien and Johnson & Johnson"

Wig 1999

Methods	Randomised clinical trial	
Participants	Country: India. Number randomised: 40. Post-randomisation drop-out(s): not stated. Revised sample size: 40. Mean age: 48.9 years. Females: 20 (50%). Number with malignancy: 24/40 (60%). Inclusion criteria: 1. Patients with obstructive jaundice. 2. Bilirubin greater than 172 micromoles per litre.	
Interventions	The patients were randomised to the following groups. Group 1: pre-operative biliary drainage (n = 20). Further details: percutaneous transhepatic biliary drainage into a sealed bag containing povidone iodine continued until bilirubin drops below 102.85 micromoles per litre. Group 2: control (n = 20).	
Outcomes	The outcomes reported were mortality and morbidity.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly allocated". Comment: the trial is described as randomised, but the method of sequence generation was not specified

Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomly allocated". Comment: the trial was described as randomised but the method used to conceal the allocation was not described
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: the trial was not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: we did not know if there were post-randomisation drop-outs or withdrawals
Selective reporting (reporting bias)	High risk	Comment: the severity of the complications was not reported.
Vested interest bias	Unclear risk	Comment: the trial did not report the source of funding.

PTC = percutaneous transhepatic cholangiography.

ERCP = endoscopic retrograde cholangio pancreatography.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Smith 1985	Randomisation by hospital file numbers, ie, quasi-randomised study

DATA AND ANALYSES

Comparison 1

Pre-operative biliary drainage versus direct surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6	520	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.71]
2 Long-term mortality			Other data	No numeric data
3 Serious morbidity	6		Rate Ratio (Fixed, 95% CI)	1.66 [1.28, 2.16]
4 Proportion of patients with serious morbidity			Other data	No numeric data
5 Hospital stay (random-effects)	2	271	Mean Difference (IV, Random, 95% CI)	4.87 [-1.28, 11.02]

Comparison 2

Stratified by method of drainage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6	520	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.71]
1.1 PTBD	4	237	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.62, 2.08]
1.2 ERCP stent	2	283	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.62, 1.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Overall morbidity	6		Rate Ratio (Fixed, 95% CI)	1.66 [1.28, 2.16]
2.1 PTBD	4		Rate Ratio (Fixed, 95% CI)	1.53 [1.00, 2.34]
2.2 ERCP stent	2		Rate Ratio (Fixed, 95% CI)	1.75 [1.25, 2.44]

Comparison 3

Stratified by proportion of patients with malignancy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6	520	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.71]
1.1 95% or more malignancy	3	209	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.70, 2.27]
1.2 Less than 95% malignancy	3	311	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.54, 1.83]
2 Overall morbidity	6		Rate Ratio (Fixed, 95% CI)	1.66 [1.28, 2.16]
2.1 95% or more malignancy	3		Rate Ratio (Fixed, 95% CI)	2.09 [1.29, 3.39]
2.2 Less than 95% malignancy	3		Rate Ratio (Fixed, 95% CI)	1.51 [1.10, 2.06]

Comparison 4

Sensitivity analysis of overall morbidity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious complications without Pitt 1985 (proximal obstruction)	5		Rate Ratio (Fixed, 95% CI)	1.77 [1.34, 2.34]
2 Serious complications without Lai 1994 (severity of complications could not be assessed)	5		Rate Ratio (Fixed, 95% CI)	1.70 [1.27, 2.26]
3 Serious complications without van der Gaag 2010 (no routine antibiotic prophylaxis)	5		Rate Ratio (Fixed, 95% CI)	1.51 [1.06, 2.16]
4 Bile leak irrespective of treatment	6		Rate Ratio (Fixed, 95% CI)	1.67 [1.29, 2.15]

Analysis 1.1. Comparison 1 Pre-operative biliary drainage versus direct surgery, Outcome 1 Mortality

Review: Pre-operative biliary drainage for obstructive jaundice

Comparison: 1 Pre-operative biliary drainage versus direct surgery

Outcome: 1 Mortality

Analysis 1.2. Comparison 1 Pre-operative biliary drainage versus direct surgery, Outcome 2 Long-term mortality

Long-term mortality

Study	
van der Gaag 2010	Hazard ratio 0.90; 95% CI 0.65 to 1.24

Analysis 1.3. Comparison 1 Pre-operative biliary drainage versus direct surgery, Outcome 3 Serious morbidity

Review: Pre-operative biliary drainage for obstructive jaundice

Comparison: 1 Pre-operative biliary drainage versus direct surgery

Outcome: 3 Serious morbidity

Analysis 1.4. Comparison 1 Pre-operative biliary drainage versus direct surgery, Outcome 4 Proportion of patients with serious morbidity

Proportion of patients with serious morbidity

Study	Proportion of patients with serious morbidity in the PBD group	Proportion of patients with serious morbidity in the direct surgery group	Statistical significance by Fisher's exact test
van der Gaag 2010	75/102 (73.5%)	37/94 (39.4%)	p<0.001

Analysis 1.5. Comparison 1 Pre-operative biliary drainage versus direct surgery, Outcome 5 Hospital stay (random-effects)

Review: Pre-operative biliary drainage for obstructive jaundice

Comparison: 1 Pre-operative biliary drainage versus direct surgery

Outcome: 5 Hospital stay (random-effects)

Analysis 2.1. Comparison 2 Stratified by method of drainage, Outcome 1 Mortality

Review: Pre-operative biliary drainage for obstructive jaundice

Comparison: 2 Stratified by method of drainage

Outcome: 1 Mortality

Analysis 2.2. Comparison 2 Stratified by method of drainage, Outcome 2 Overall morbidity

Review: Pre-operative biliary drainage for obstructive jaundice

Comparison: 2 Stratified by method of drainage

Outcome: 2 Overall morbidity

Analysis 3.1. Comparison 3 Stratified by proportion of patients with malignancy, Outcome 1 Mortality

Review: Pre-operative biliary drainage for obstructive jaundice

Comparison: 3 Stratified by proportion of patients with malignancy

Outcome: 1 Mortality

Analysis 3.2. Comparison 3 Stratified by proportion of patients with malignancy, Outcome 2 Overall morbidity

Review: Pre-operative biliary drainage for obstructive jaundice

Comparison: 3 Stratified by proportion of patients with malignancy

Outcome: 2 Overall morbidity

Analysis 4.1. Comparison 4 Sensitivity analysis of overall morbidity, Outcome 1 Serious complications without Pitt 1985 (proximal obstruction)

Review: Pre-operative biliary drainage for obstructive jaundice

Comparison: 4 Sensitivity analysis of overall morbidity

Outcome: 1 Serious complications without Pitt 1985 (proximal obstruction)

Analysis 4.2. Comparison 4 Sensitivity analysis of overall morbidity, Outcome 2 Serious complications without Lai 1994 (severity of complications could not be assessed)

Review: Pre-operative biliary drainage for obstructive jaundice

Comparison: 4 Sensitivity analysis of overall morbidity

Outcome: 2 Serious complications without Lai 1994 (severity of complications could not be assessed)

Analysis 4.3. Comparison 4 Sensitivity analysis of overall morbidity, Outcome 3 Serious complications without van der Gaag 2010 (no routine antibiotic prophylaxis)

Review: Pre-operative biliary drainage for obstructive jaundice

Comparison: 4 Sensitivity analysis of overall morbidity

Outcome: 3 Serious complications without van der Gaag 2010 (no routine antibiotic prophylaxis)

Analysis 4.4. Comparison 4 Sensitivity analysis of overall morbidity, Outcome 4 Bile leak irrespective of treatment

Review: Pre-operative biliary drainage for obstructive jaundice

Comparison: 4 Sensitivity analysis of overall morbidity

Outcome: 4 Bile leak irrespective of treatment

Appendix 1. Search strategies

Database	Time span	Search strategy used
Cochrane Hepato-Biliary Group Controlled Trials Register	February 2012.	((liver or hepat* or pancrea* or bile duct or choledoch*) and (cancer* or neoplasm* or malignan* or tumour* or tumor*)) or cholangiocarcinoma or cholesta* or icter* or jaundice) AND (drain* or stent* or cholangio* or sphincterotomy* or ptc or ptbd or ERCP or endoscopic*)
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Issue 1, 2012.	#1 MeSH descriptor Jaundice, Obstructive explode all trees #2 MeSH descriptor Pancreatic Neoplasms explode all trees #3 MeSH descriptor Liver Neoplasms explode all trees #4 MeSH descriptor Bile Duct Neoplasms explode all trees #5 MeSH descriptor Ampulla of Vater explode all trees #6 MeSH descriptor Cholangiocarcinoma explode all trees #7 MeSH descriptor Cholestasis explode all trees #8 ((liver or hepat* or pancrea* or bile duct or choledoch*) and (cancer* or neoplasm* or malignan* or tumour* or tumor*)) or cholangiocarcinoma or cholesta* or icter* or jaundice #9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) #10 MeSH descriptor Cholangiography explode all trees #11 MeSH descriptor Sphincterotomy, Endoscopic explode all trees #12 MeSH descriptor Sphincterotomy, Transhepatic explode all trees #13 MeSH descriptor Stents explode all trees #14 MeSH descriptor Preoperative Care explode all trees #15 MeSH descriptor Drainage explode all trees #16 drain* or stent* or cholangio* or sphincterotomy* or ptc or ptbd or ERCP or endoscopic* #17 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16) #18 (#9 AND #17)
MEDLINE (OvidSP)	1948 to February 2012.	1. exp Jaundice, Obstructive/ 2. exp Pancreatic Neoplasms/ 3. exp Liver Neoplasms/ 4. exp Bile Duct Neoplasms/ 5. exp Ampulla of Vater/ 6. exp Cholangiocarcinoma/ 7. exp Cholestasis/ 8. (((liver or hepat* or pancrea* or bile duct or choledoch*) and (cancer* or neoplasm* or malignan* or tumour* or tumor*)) or cholangiocarcinoma or cholesta* or icter* or jaundice). af 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. exp Cholangiography/ 11. exp Sphincterotomy, Endoscopic/ 12. exp Sphincterotomy, Transhepatic/

Database	Time span	Search strategy used
		13. exp Stents/ 14. exp Preoperative Care/ 15. exp Drainage/ 16. (drain* or stent* or cholangio* or sphincterotomy* or ptc or ptbd or ERCP or endoscopic*).af 17. 10 or 11 or 12 or 13 or 14 or 15 or 16 18. 9 and 17 19. randomised controlled trial.pt. 20. controlled clinical trial.pt. 21. randomized.ab. 22. placebo.ab. 23. drug therapy.fs. 24. randomly.ab. 25. trial.ab. 26. groups.ab. 27. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 28. exp animals/ not humans.sh. 29. 28 not 27 30. 18 and 29
EMBASE (OvidSP)	1980 to February 2012.	1. exp obstructive jaundice/ 2. exp pancreas tumor/ 3. exp liver tumor/ 4. exp bile duct tumor/ 5. exp Vater papilla/ 6. exp bile duct carcinoma/ 7. exp cholestasis/ 8. (((liver or hepat* or pancrea* or bile duct or choledoch*) and (cancer* or neoplasm* or malignan* or tumour* or tumor*)) or cholangiocarcinoma or cholesta* or icter* or jaundice). af 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. exp cholangiography/ 11. exp endoscopic sphincterotomy/ 12. exp biliary tract surgery/ 13. exp stent/ 14. exp preoperative care/ 15. exp biliary tract drainage/ 16. (drain* or stent* or cholangio* or sphincterotomy* or ptc or ptbd or ERCP or endoscopic*).af 17. 10 or 11 or 12 or 13 or 14 or 15 or 16 18. exp crossover-procedure/ or exp double-blind procedure/ or exp randomised controlled trial/ or single-blind procedure/ 19. (random* or factorial* or crossover* or placebo*).af. 20. 18 or 19 21. 9 and 17 and 20
Science Citation Index Expanded (ISI Web of Knowledge)	1970 to February 2012.	# 1 TS=((liver or hepat* or pancrea* or bile duct or choledoch*) and (cancer* or neoplasm* or malignan* or tumour* or tumor*)) or cholangiocarcinoma or cholesta* or icter* or jaundice) # 2 TS=(drain* or stent* or cholangio* or sphincterotomy* or ptc or ptbd or ERCP or endoscopic*) # 4 #3 AND #2 AND #1 # 3 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*)
metaRegister of Controlled Trials (http://www.controlled-trials.com/mrct/)	February 2012.	(icter* OR jaundice) AND (drain* OR stent*)

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 3, 2008

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol had the title 'Preoperative biliary drainage for malignant obstructive jaundice' (Gurusamy KS, Wang C. Preoperative biliary drainage for malignant obstructive jaundice (Protocol). Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD005444. DOI: 10.1002/14651858.CD005444.).

We have modified the title of the review to read: 'Pre-operative biliary drainage for obstructive jaundice' as we felt that the purpose of the preoperative biliary drainage is the same whether it was done for benign causes or malignant causes. We have modified the inclusion and exclusion criteria accordingly. However, we have performed a subgroup analysis to evaluate the beneficial and harmful effects of pre-operative biliary drainage in malignant obstructive jaundice.

Differences between the previous review version and this updated review version

We have revised the methods according to the currently available version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We have revised the discussion in line with the GRADE handbook for grading quality of evidence and the strength of a recommendation (Schünemann 2009).

WHAT'S NEW

Last assessed as up-to-date: 10 February 2012.

Date	Event	Description
13 April 2011	New citation required and conclusions have changed	Conclusions changed.
7 October 2010	New search has been performed	New searches were performed, and one new trial was identified and added

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

Pre-operative biliary drainage versus direct surgery for obstructive jaundice

Patient or population: patients with obstructive jaundice.

Settings: secondary or tertiary care setting.

Intervention: pre-operative biliary drainage versus direct surgery.

Outcomes	Illustrative comparative risks* (95% CI)			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk		Corresponding risk				
	Control	Pre-operative biliary drainage versus direct surgery					
Mortality	133 per 1000	149 per 1000 (97 to 228)	RR 1.12 (0.73 to 1.71)	520 (6 studies)	⊕⊕⊕⊕ very low ^{1,2,3}		
Morbidity ICH-GCP classification	361 per 1000	599 per 1000 (462 to 780)	Rate ratio 1.66 (1.28 to 2.16)	503 (6 studies)	⊕⊕⊕⊕ very low ^{1,3,4}		

* The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

¹ All trials were of high risk of bias.

² Overlaps 1 and 0.75 or 1.25.

³ There were few trials to assess publication bias.

⁴ I² was 44%. There was also minimal overlap of confidence intervals between some of the trials.

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* Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

Biliary drainage before major operations in patients with obstruction of the bile duct

The liver has various functions, including the production and storage of substances necessary for the sustenance of life. It processes toxic substances (including those that are produced within the body because of the breakdown of old red cells) and plays a role in the excretion of these processed toxic substances. It produces bile, which contains substances necessary for the digestion of food. The bile is temporarily stored in the gallbladder and reaches the small bowel via the bile duct, usually in response to a stimulus such as ingestion of fatty food. The processed toxic substances are transported in the bile. These processed toxic substances are eventually excreted when the person opens his or her bowel. When there is obstruction to the flow of bile, the breakdown products of red cells can accumulate and cause yellowish discolouration of the skin and other linings in the body such as the white of the eyeball and the undersurface of the tongue. This results in a form of jaundice called obstructive jaundice. The obstruction to the bile flow is usually caused by stones in the common bile duct. These stones can originate from the gallbladder or from common bile duct stones. The majority of such stones can be treated endoscopically. However, a small proportion of the stones require surgery for removal. Other major causes of biliary obstruction include narrowing of the bile duct resulting from inflammation caused by stones, injury to the bile duct during operations to remove the gallbladder, and cancer of the bile duct, pancreas (an organ situated behind and below the stomach that secretes the digestive juices necessary for the digestion of food in addition to containing the cells that secrete insulin in order to maintain blood sugar levels), or the upper part of the small bowel called the duodenum. Operative removal is currently the only curative treatment available for these cancers. Such operations are typically major operations. However, the presence of toxic substances because of obstruction to the bile flow can result in physiological disturbances. Some surgeons perform certain procedures to temporarily drain the bile before performing the major operation to remove biliary obstruction due to stones, inflammation, or cancer. These pre-operative procedures can be done endoscopically (by introducing an instrument equipped with a camera through the mouth and into the small intestine and then inserting a small drainage tube through that instrument and past the obstruction in the bile duct) or under X-ray or other forms of image guidance via the liver. However, other surgeons argue that the temporary procedures to drain the bile are not necessary and that one should perform surgery directly. We sought evidence from randomised clinical trials only regarding this controversy. Such studies, when conducted properly, provide the best evidence. Two authors independently identified the trials and obtained the information from the trials.

We included six trials involving 510 patients for this review. The number of patients included in the trials varied from 40 to 202. All trials had a high risk of bias, that is, the trials may overestimate benefits and underestimate harms. There was no significant difference in risk of death between the two groups. The rate of serious complications was higher in the patients who underwent biliary drainage prior to operation compared with

those who underwent surgery directly. The quality of life was not reported in any trial. There was no significant difference in the length of hospital stay between the two groups. The costs were not reported in any of the trials. Based on the currently available best evidence, there is no justification for the use of routine drainage of bile before a major operation in patients with obstruction to the flow of bile. Routine biliary drainage should not be funded and may result in litigations. Furthermore, well designed trials with low risk of systematic errors and low risk of random errors (low risk of play of chance) may be necessary.

Figure 1.
Study flow diagram.

Figure 2.

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Vested interest bias
Hatfield 1982	?	?	-	-	-	?
Lai 1994	?	?	-	+	-	?
McPherson 1984	?	?	-	-	-	?
Pitt 1985	+	?	-	-	-	?
van der Gaag 2010	+	+	+	-	+	-
Wig 1999	?	?	-	?	-	?

Figure 3.

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 4.

Trial sequential analysis of preoperative biliary drainage versus direct surgery for obstructive jaundice on mortality. The required information size of 11,130 patients was calculated based on a prevalence of death of 13% in the surgery group; a relative risk reduction of 20%; an alpha of 5%; and a beta of 20%. The cumulated Z-curve shows that only a small proportion, that is 520 patients, of the required number of patients to demonstrate differences in mortality has been recruited in all the clinical trials comparing pre-operative biliary drainage and direct surgery and that no statistical significant difference has been observed.