Management of Delayed Postoperative Hemorrhage After Pancreaticoduodenectomy

A Meta-analysis

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Objective: To determine whether interventional radiology (IR) or laparotomy (LAP) is the best management of delayed postoperative hemorrhage (DPH) after pancreaticoduodenectomy.

Data Source: We undertook an electronic search of MEDLINE and selected for analysis only original articles published between January 1, 1990, and December 31, 2007.

Study Selection: Two of us independently selected studies reporting on clinical presentation and incidence of postoperative DPH and the following outcomes: complete hemostasis, morbidity, and mortality.

Data Extraction: Two of us independently performed data extraction. Data were entered and analyzed by means of dedicated software from The Cochrane Collaboration. A random-effects meta-analytical technique was used for analysis.

Data Synthesis: One hundred sixty-three cases of DPH after pancreaticoduodenectomy were identified from the literature. The incidence of DPH after pancreaticoduodenectomy was 3.9%. Seventy-seven patients (47.2%) underwent LAP; 73 (44.8%), IR; and 13 (8%), conservative treatment. On meta-analysis comparing LAP vs IR for DPH, no significant difference was found between the 2 treatment options for complete hemostasis (73% vs 76%; P = .23), mortality (43% vs 20%; P = .14), or morbidity (77% vs 35%; P = .06).

Conclusions: This meta-analysis, although based on data from small case series, is unable to demonstrate any significant difference between LAP and IR in the management of DPH after pancreaticoduodenectomy. The management of this life-threatening complication is difficult, and the appropriate treatment pathway ultimately will be decided by the clinical status of the patient and the institution preference.

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Methods

An electronic search of MEDLINE was undertaken using the key words delayed hemorrhage, delayed bleeding, delayed arterial hemorrhage, delayed arterial bleeding, transcatheter arterial embolization, covered stents, pancreatic resection, and pancreaticoduodenectomy in
various combinations. Only original articles published between January 1, 1990, and December 31, 2007, were selected for analysis. The search terms were identified in the title, abstract, or medical subject heading (MeSH).

Two authors independently selected studies reporting on DPH after pancreaticoduodenectomy. One of us (P.L.) extracted and summarized the details of the studies, including the type of surgery, number of patients with DPH, clinical presentation, primary treatment, and its outcome. These details were checked by a second, independent author (S.E.K.) to avoid data input errors.

The patient-relevant outcomes were complete hemostasis, morbidity, and mortality. For this meta-analysis, mortality included any death and morbidity included any complication occurring within 3 months after pancreaticoduodenectomy. The definition of DPH used in the literature is variable. Because of this, we reanalyzed the data to look at potential break points in the time to occurrence and the treatment modality. The fifth postoperative day or later was identified and used as the most appropriate break point for DPH based on the published data.

Quantitative data were entered into the computer by one of us (P.L.) and analyzed using commercially available statistical software (SPSS for Windows, version 12.0 [SPSS Inc, Chicago, Illinois] and Review Manager, version 4.2 [The Cochrane Collaboration, Software Update, Oxford, England]).

Data entry and analysis were checked by a second author (S.E.K.). The meta-analysis was performed according to recommendations from The Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines. Results are expressed as median or range, unless otherwise indicated. For each outcome, a meta-analysis was performed, using an odds ratio as the summary statistic calculated by means of a random-effects model with 95% confidence intervals. The Mantel-Haenszel method was used to combine the odds ratio for the outcomes of interest by means of a random-effects meta-analytical technique. In a random-effects model, it is assumed that there is variation between studies and the calculated odds ratio; thus, it produces a more conservative value.

The odds ratios represent the odds of an adverse event occurring in the LAP group compared with the interventional radiology (IR) group. An odds ratio of less than 1 favored LAP, and the point estimate of the odds ratio was considered to be statistically significant at the level of \( P < .05 \), if the 95% confidence interval did not include the value 1. When a large number of comparisons are made on a small number of cases with inadequate statistical power, a large confidence interval is usually anticipated.

Our search identified a total of 163 cases of DPH after pancreaticoduodenectomy (Table 1). The incidence of DPH after pancreaticoduodenectomy was 3.9%. The timing of this complication ranged from 5 to 206 (median, 26) days after pancreaticoduodenectomy. The clinical presentation included intra-abdominal hemorrhage (n = 101), hematemesis and/or melena (n = 46), and both (n = 16). Sentinel bleeding, defined as 1 or more episodes of minor bleeding preceding a major hemorrhage by 6 hours to 10 days, was described in 54 patients (33.1%). When documented, 107 patients with DPH (65.6%) had associated intra-abdominal abscess and/or anastomotic leak. In 53 cases of DPH (32.5%), an underlying pseudoaneurysm was responsible. Of the 163 patients reported to have DPH, 77 (47.2%) underwent LAP, 73 (44.8%) underwent IR, and 13 (8.0%) were treated conservatively (Table 2). Among the patients treated conservatively, one died of hypovolemic shock and another of further gastrointestinal tract bleeding associated with sepsisemia. The remaining 11 patients in that group had no further bleeding.

### Table 1. Incidence and Clinical Onset of Reported Cases of DPH After Pancreaticoduodenectomy

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of DPH</th>
<th>Bleeding</th>
<th>Type of DPH, IAH/GB/Both</th>
<th>Sentinel</th>
<th>IAA and/or Anostomotic Leak</th>
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<td>4/0/7</td>
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<tr>
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<td>81</td>
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Abbreviations: DPH, delayed postoperative hemorrhage; GB, gastrointestinal tract bleeding; IAA, intra-abdominal abscess; IAH, intra-abdominal hemorrhage; NS, not specified.

Data are expressed as number of cases.
META-ANALYSIS OF LAP VS IR FOR COMPLETE HEMOSTASIS OF DPH AFTER PANCREATICODUODENECTOMY

Only 2 studies34,35 did not report on complete hemostasis after LAP or IR (Figure 1). The 22 patients from these 2 studies, along with 13 patients treated conservatively, were excluded from this analysis.

Complete hemostasis was obtained in 46 of 63 patients (73%) undergoing LAP and in 56 of 73 (77%) undergoing IR (Figure 1). On statistical analysis, no significant difference was found between LAP and IR in achieving complete hemostasis of DPH after pancreaticoduodenectomy (P=.23). In the 35 patients with rebleeding after primary treatment, 25 underwent LAP and 10 underwent IR to achieve hemostasis.
META-ANALYSIS OF LAP VS IR FOR MORTALITY AND MORBIDITY

All 20 studies reported on morbidity and mortality after LAP or IR treatment of DPH. Thirteen patients underwent conservative treatment and were excluded. Fifty-four of 77 patients undergoing LAP (70%) and 26 of 73 undergoing IR (36%) had complications (Figure 2). Among the 93 posttreatment complications, there were 5 cases (5%) of hepatic failure after IR and 1 case (1%) after LAP. Four of these 6 patients who developed hepatic failure after primary treatment died during hospitalization. However, on meta-analysis, only a marginally significant difference was found for morbidity between LAP and IR in the treatment of DPH after pancreaticoduodenectomy (\( P = .05 \)).

Fifty of 163 patients with DPH (30.7%) died after treatment. Reported causes of death after LAP were hemorrhagic shock, septic shock, disruption of the pancreaticojejunostomy, erosion into the adjacent superior mesenteric artery, disseminated intravascular coagulation, and multiple organ failure. Septic shock, hemorrhagic shock, hepatic failure, and multiple organ failure were the reported causes of death after IR. Death occurred in 33 of the 77 patients undergoing LAP (43%) and only 15 of the 73 undergoing IR (20%) (Figure 3). Statistical analysis did not demonstrate any significant difference in mortality between LAP and IR in the treatment of DPH after pancreaticoduodenectomy (\( P = .13 \)).

COMMENT

Although DPH after pancreatic resection is a well-recognized complication, it is relatively uncommon.\(^{15,30}\) As a result, its management remains unclear. From the literature we identified 163 cases of DPH after pancreaticoduodenectomy (Table 1). The incidence of DPH after pancreaticoduodenectomy was found to be 3.9%, with a third of patients with this complication dying of it. The pathogenesis of DPH after pancreaticoduodenectomy appears to be multifactorial. In pancreaticoduodenectomy, regional lymphadenectomy and extensive vascular skeletonization are often performed, making vessels vulnerable to erosion due to local sepsis secondary to abscess, pancreatic fistula, or anastomotic leakage.\(^{17,18,20,27}\)

From our review, we found that almost two-thirds (65.6%) of the cases of DPH were associated with intra-abdominal abscess or anastomotic leak, and pseudoaneurysms were found to be involved in DPH after pancreaticoduodenectomy in approximately one-third of cases (53 of 163 [32.5%]). In 33.1% of reported cases, sentinel bleeding occurred, which is where 1 or more episodes of minor bleeding preceded a major DPH. A major DPH was defined as a significant drop in hemoglobin level or as hemodynamic instability necessitating blood transfusion.\(^{9,15}\) This definition emphasizes that any episode of hemorrhage, regardless of its severity, should be investigated aggressively in this group of patients.

From the literature, when reported, we found that less than one-third of patients (28.2%) presented with gastrointestinal tract bleeding, and approximately two-thirds (61.3%) presented with intra-abdominal bleeding. Gastrointestinal tract hemorrhage is often due to bleeding from a marginal ulcer at the anastomosis, the suture line, or a ruptured pseudoaneurysm secondary to an anastomotic leak. On the other hand, intra-abdominal hemorrhage is usually detected by noticing blood in an abdominal drain and is often associated with a leak from the pancreatic anastomosis.\(^{4,20}\) Endoscopy, which is usually used as a first diagnostic tool when upper gastrointestinal tract bleeding is suspected, may fail to pinpoint the site of hemorrhage, and positive findings such as erosive gastritis on endoscopy can be dangerously misleading and result in a delayed intervention or, in the worst cases, death.\(^{4,15,18,21}\)

Historically, LAP has probably been the first choice of treatment for DPH after pancreaticoduodenectomy.\(^{15,30}\) Laparotomy allows hemostasis (by ligation or underrunning of the vessels or pseudoaneurysms) to be combined with treatment of the factors contributing to DPH, such as anastomotic disruption or intra-abdominal collections. In cases of pancreatic leak or disrupted anastomosis, better mortality outcomes have been reported for lesser procedures, such as taking down and oversewing the pancreatic stump or occluding the pancreatic duct, when compared with aggressive completion pancreatectomy.\(^{16,23,41,42}\) However, during the past decade, a number of publications have reported encouraging results after management of DPH by IR.\(^{17,21,24,26,27,37}\)

From the published cases in the literature, LAP was performed in 47.2% of cases with DPH, and 44.8% underwent IR. The meta-analysis did not reveal a significant difference between IR and LAP in successfully arresting hemorrhage (\( P = .23 \)). No significant difference in posttreatment complications was found when DPH had been managed by LAP vs IR (\( P = .06 \)), despite 70% of patients experiencing a complication in the LAP group compared with 36% in the IR group. A significant difference in death events between the 2 treatment options was also not found, despite 43% of patients dying when treated with LAP compared with 21% dying when treated with IR. The finding of higher morbidity and mortality in the patients treated with LAP is not unexpected considering the invasiveness of this strategy in patients already weakened by their initial surgical resection and debilitated further by the development of sepsis or anastomotic breakdown that then predisposed them to developing DPH.

Selective visceral angiography of the celiac and superior mesenteric arteries has been shown to be the single most valuable examination to elucidate the bleeding site.\(^{45-47}\) However, angiography has limitations when the bleeding is venous, diffuse, or intermittent.\(^{45}\) Transcatheter arterial embolization has been shown to be a safe and effective first-line treatment for ruptured pseudoaneurysm.\(^{48,50}\) Drawbacks of this procedure can be the accidental or intentional occlusion of the hepatic artery, which can lead to cholangitis, hepatic abscess, or fatal hepatic failure. From the published data, we found 5 cases (5%) of hepatic failure after IR and 1 case (1%) after LAP in the treatment of DPH (Table 2). However, the recent use of covered stents in the management of DPH may prove to be a useful solution for arresting hemorrhage while...
preserving hepatic artery perfusion and may further establish the role of IR in the management of DPH after pancreaticoduodenectomy. To our knowledge, no prospective randomized clinical trial comparing LAP with IR in the management of DPH after pancreaticoduodenectomy has been conducted.

Figure 2. Forest plots of overall morbidity for interventional radiology (IR) vs laparotomy (LAP) in delayed postoperative hemorrhage after pancreaticoduodenectomy. Squares indicate the point estimates of the treatment effect (odds ratio [OR]), with 95% confidence intervals (CIs) indicated by horizontal bars. The diamond represents the summary estimate from the pooled studies with 95% CIs.

Figure 3. Forest plots of overall mortality for interventional radiology (IR) vs laparotomy (LAP) in delayed postoperative hemorrhage after pancreaticoduodenectomy. Squares indicate the point estimates of the treatment effect (odds ratio [OR]), with 95% confidence intervals (CIs) indicated by horizontal bars. The diamond represents the summary estimate from the pooled studies with 95% CIs.
ducted to date, largely owing to the limited number of patients presenting with this postoperative complication. Therefore, there is currently no evidence to suggest that one strategy is superior to the other. This meta-analysis, although based on small case series of DPH after pancreaticoduodenectomy, has not been able to demonstrate that IR is significantly more advantageous than LAP. Based on the result of the present study, the management of this life-threatening complication ultimately will be dictated by the clinical status of the patient and the institutional preference, with IR as the potential first-line less aggressive invasive investigation and treatment for hemodynamically stable patients and a more aggressive surgical approach as an imminent and/or definitive option when others have failed.

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**INVITED CRITIQUE**

“Lies, damn lies, and statistics”: This famous phrase could be used to describe recent forays into evidence-based medicine, where the filtering of disparate data from small, underpowered studies using the mechanics of a meta-analysis conveys to the reader a higher degree of precision than is warranted. Take the meta-analysis of DPH after pancreaticoduodenectomy by Limongelli and colleagues published in this issue of the *Archives*. The authors have followed rigorous steps for identifying the relevant published literature, combining them, and applying appropriate statistical analysis using a random-effects model to examine the overall results. They performed an appropriate, well-done textbook study, even including oversight on their data collection and transfer. What this method fails to convey is that, despite this structure, it remains a composite of small numbers of patients (largest series, 22 patients), treated by a large number of heterogeneous surgeons on several continents who possessed widely disparate expertise and variable access to dissimilar levels of care. It seems inconceivable to me that a P value, no matter how rigorously derived, is capable of accurately adjusting for all of these variables and mathematically accepting one method of treatment over another. It may be time to accept the fact that there are certain disease states encountered not infrequently in biomedical science, particularly the discipline of surgery, that present insurmountable limitations when one attempts to derive a single truth for all patients. Is this the elusive art that we all recognize as a major component of our discipline? As the authors correctly conclude in their discussion, “The management of this life-threatening complication ultimately will be dictated by the clinical status of the patient and the institutional preference.” What they failed to mention is, “despite the P value assigned.”

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