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Variables Associated with Outcome in Dogs Undergoing Extrahepatic Biliary Surgery: 60 Cases (1988–2002)

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Objective—To report clinical findings and define clinical variables associated with outcome in dogs undergoing extrahepatic biliary surgery.

Study Design—Retrospective study.

Animals—Sixty dogs that had extrahepatic biliary tract surgery.

Results—Primary diagnoses included necrotizing cholecystitis (36 dogs, 60%), pancreatitis (12 dogs, 20%), neoplasia (5 dogs, 8%), trauma (4 dogs, 7%), and gallbladder rupture from cholelithiasis without necrotizing cholecystitis (3 dogs, 5%). Bile peritonitis occurred in 19 (32%) dogs with necrotizing cholecystitis, 4 dogs with trauma, and 3 dogs with cholelithiasis without evidence of necrotizing cholecystitis. Cholecystectomy (37 dogs, 62%) and cholecystoduodenostomy (14 dogs, 23%) were the 2 most commonly performed procedures. Median hospitalization for survivors was 5 days (range, 1–15 days). There were 43 surviving dogs (72%) and 17 nonsurvivors (28%, 4 died, 13 euthanatized). Presence of septic bile peritonitis ($P = .038$), elevation in serum creatinine concentration ($P = .003$), prolonged partial thromboplastin times (PTTs; $P = .003$), and lower postoperative mean arterial pressures ($P = .0001$) were significantly associated with mortality.

Conclusions—Extrahepatic biliary surgery is associated with high mortality and a relatively long hospitalization time for survivors. Cholecystectomy and cholecystoduodenostomy were the most common surgical procedures to treat the 4 major biliary problems (necrotizing cholecystitis, pancreatitis, neoplasia, and trauma) observed in this cohort of dogs. The relatively high mortality rate likely reflects the underlying diseases and their effects on the animal (septic bile peritonitis, higher serum creatinine, prolonged PTT, and lower postoperative mean arterial pressure) rather than complications of surgery.

Clinical Relevance—Septic bile peritonitis, preoperative elevated creatinine concentration, and immediate postoperative hypotension in dogs undergoing extrahepatic biliary tract surgery are associated with a poor clinical outcome. Adequate supportive care and monitoring in the perioperative period is critical to improve survival of dogs with extrahepatic biliary disease.

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Key words: bile peritonitis, cholecystectomy, cholecystitis, cholecystoduodenostomy, cholelithiasis, dog, extrahepatic biliary surgery.

INTRODUCTION

EXTRAHEPATIC BILIARY tract diseases occur less frequently in dogs than hepatic parenchymal conditions. Several human studies have identified preoperative factors that increase patients’ risk of perioperative mortality. These include malignancy, age (> 60 years), fever, leukocytosis, azotemia, hypoalbuninemia, hyperbilirubinemia, anemia, and increased serum alkaline phosphatase. Advances in surgical technique and supportive care have improved perioperative outcomes in humans. As surgical techniques and medical management have improved in dogs, the morbidity and mortality associated with extrahepatic biliary surgery have decreased.
phosphatase (ALP). However, the clinical variables associated with outcome have not been investigated extensively in dogs.

Therefore, our aims were: to report diagnoses, clinical progression, clinicopathologic and microbiologic findings, surgical procedures, and outcome in dogs undergoing extrahepatic biliary surgery; and to define clinical variables associated with outcome in this cohort of dogs.

MATERIALS AND METHODS

Criteria for Inclusion

Medical records of dogs that had biliary tract surgery between 1988 and 2002 were reviewed. Dogs included in the study had extrahepatic biliary surgery, a complete medical record with a detailed surgical report, and definitive information about outcome.

Variables reviewed included previous medical history, signalment, physical examination findings, clinicopathologic data (complete blood count, serum biochemistry, and coagulation profiles), lowest mean intraoperative and postoperative arterial blood pressures (LMAp, indirect and direct measurements), surgical findings, bacterial culture results, and histologic evaluation of tissue biopsies. A complete blood count and serum chemistry profile were performed in all dogs within the 24-hour presurgical period.

Surgical Procedures

Each dog had a complete exploratory celiotomy. The liver, biliary tract, and surrounding tissues were examined for signs of inflammation, necrosis, cholelithiasis, inspissated bile, neoplasia, and trauma. If the gallbladder was severely diseased or ruptured and if patency of the common bile duct could be confirmed, cholecystectomy was performed. Patency of the common bile duct was determined by manual expression of the gallbladder, normograde catheterization of the common bile duct through a cholecystotomy incision, or retrograde passage of a catheter through the major duodenal papilla via a duodenotomy incision. A biliary rerouting procedure (cholecystoduodenostomy, cholecystojejunostomy, or tube stenting) was performed if there was evidence of bile flow obstruction.

Incisional or excisional biopsy was performed in any dog with an abdominal mass. Gallbladder mucosa, bile specimens, or abdominal fluid were submitted for bacterial culture and antibiotic susceptibility testing at the surgeons' discretion. All tissue samples were preserved in buffered 10% formalin, embedded in paraffin, sectioned at 6 μm, and stained with hematoxylin and eosin for histologic examination.

Outcome Groups

Survivors were defined as dogs that were alive 2 weeks after surgery and returned to the hospital for follow-up examination and suture removal. Nonsurvivors were dogs that died or were euthanatized in this 2-week period from causes related to the underlying disease process or complications associated with surgery.

Two weeks was chosen to define survival because we had definitive follow-up information on all dogs for 2 weeks and several dogs died or were euthanatized within 2 weeks because of complications that could reasonably be linked to surgery or underlying disease. Dogs that were discharged and were normal at suture removal were assumed to have recovered from the direct effects of surgery.

Statistical Analysis

Interval (continuous) variables were assessed for normality by visual inspection and the Shapiro–Wilks test. Normally distributed variables were described using mean ± standard deviation whereas the median value was used for non-normally distributed variables. Student's t-test or the Mann–Whitney test were used to compare continuous variables between outcome groups depending upon data distribution. Dichotomous or categorical variables were expressed as proportions or percentages and the Fisher's exact test was used to compare proportions between outcome groups. A P value < .05 was considered significant. All statistical assessments were performed using a statistics software program (Stata 7.0 for Windows, College Station, TX).

RESULTS

Signalment

Sixty dogs met the inclusion criteria. There were 19 (32%) mixed breed dogs, 6 (10%) German Shepard dogs, 5 (8%) Shetland sheep dogs, 4 (7%) Cocker Spaniels, 4 (7%) Golden Retrievers, 4 (7%) Labrador Retrievers, and 1 each of 18 other breeds. There were 34 females (57%; 29 spayed, 5 intact) and 26 males (43%; 18 castrated, 8 intact). There were no significant differences between outcome groups for breed or sex. Mean age for survivors (7.7 ± 3.2 years) was not significantly different from nonsurvivors (9.6 ± 3.9 years; P = .0565).

History and Physical Examination Findings

Presenting complaints included anorexia (n = 60), lethargy (60), vomiting (58), and diarrhea (16). Icterus was observed in 31 dogs. Twelve dogs had heart rates > 120 b.p.m., and 23 dogs had rectal temperatures > 103°F. Mean time between onset of clinical signs and surgery was 12.4 days (range, 2 hours–210 days).

Clinical Laboratory and Blood Pressure Findings

Significant differences were not noted between outcome groups for most variables (P values ranging from .059 to .99). Nonsurvivors had a significantly elevated serum creatinine concentration (P = .003) and
prolongation in partial thromboplastin time (PTT) ($P = .003$) compared with survivors (Table 1).

Median lowest intraoperative blood pressure for 57 dogs was 60 mm Hg (range, 38–96 mm Hg) with no significant difference between outcome groups. However, the lowest postoperative blood pressure was significantly ($P = .0001$) less for nonsurvivors compared with surviving dogs.

**Characterization of Biliary Disease**

Extrahepatic biliary diseases were necrotizing cholecystitis (36 dogs), pancreatitis and associated periductal fibrosis and abscesses (12), neoplasia (5), trauma (4), and gallbladder rupture without necrotizing cholecystitis (3). Thirteen of the 36 dogs with necrotizing cholecystitis had evidence of cholelithiasis.

Thirty-two dogs had evidence of an extrahepatic biliary tract obstruction. The most common cause of extrahepatic biliary tract obstruction was necrotizing cholecystitis secondary to cholelithiasis (13); other causes included pancreatitis (12) and neoplasia (2). Gallbladder biopsy findings (44 dogs) were necrotizing cholecystitis (36) and acute cholecystitis (8).

**Bile Peritonitis**

Twenty-six dogs (42%) had bile leak into the peritoneal space. Of these, 19 dogs had necrotizing cholecystitis and 3 had extrahepatic biliary tract obstructions secondary to cholelithiasis without necrotizing cholecystitis. Four dogs had traumatic biliary leakage; in 2 dogs, the common bile duct was ruptured, in 1 dog the common bile duct and right hepatic duct were ruptured, and in 1 dog the common bile duct and left hepatic duct were ruptured. Eight dogs (31%) with bile peritonitis died. Eleven dogs with biliary leakage had septic (bacterial culture positive) peritoneal fluid and 15 were sterile (culture negative). Six of 11 dogs (55%) with septic bile peritonitis died and 2 of 15 dogs (13%) with sterile bile peritonitis died. Presence of septic bile peritonitis was significantly associated with mortality ($P = .038$; Table 2).

**Microbiology Results**

Twenty-seven of 54 (50%) bacteriologic cultures of the abdominal effusion or bile were positive. Nine dogs had >1 organism cultured. Bacteria included *Escherichia coli* (n = 11), *Clostridium* spp. (9), *Staphylococcus* spp. (7), *Enterococcus* spp. (4), *Propionobacterium* spp. (3), *Pseudomonas* spp. (1), and *Streptococcus* spp. (1). Outcome was not associated with type of bacteria or isolation of multiple organisms.

**Surgery**

Cholecystectomy was performed in 37 dogs, cholecystoduodenostomy in 14, cholecystojejunostomy in 7, cholecystotomy in 1, and hepatic duct ligation in 1 dog. None of the surgical procedures was significantly associated with outcome ($P = .55$).

**Outcome**

There were 17 (28%) nonsurvivors (4 died, 13 euthanatized). Survival rates for each category of biliary disease were: 27 (75%) dogs with necrotizing cholecystitis, 4 (80%) with neoplasia, 6 (50%) with pancreatitis, 4 (100%) with trauma, and 2 (67%) with cholelithiasis and acute gallbladder rupture. There was no significant difference in survival between groups. Ten of 32 dogs (31%) with extrahepatic biliary tract obstruction were nonsurvivors whereas 7/28 (25%) dogs with nonobstructive disease (cholecystitis and trauma) were nonsurvivors. Four dogs (7%) died immediately postoperatively (cardiac arrest) and 13 (22%) were euthanatized postoperatively for reasons including disseminated intravascular coagulation.

**Table 1.** Perioperative Clinicopathologic Data for 60 Dogs with Extra-Hepatic Biliary Tract Disease Treated Surgically and Association with Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Interval</th>
<th>Surviving Dogs</th>
<th>Nonsurviving Dogs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Abnormal</td>
<td>Abnormal</td>
<td>With Abnormal</td>
<td>Abnormal</td>
</tr>
<tr>
<td></td>
<td>Results</td>
<td>Range</td>
<td>Results</td>
<td>Range</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.7–1.8 mg/dL</td>
<td>3 (6%)</td>
<td>7 (41%)</td>
<td>0.5–3.8 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5–3.8 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTT % increase, 0–25</td>
<td>3 (8.8%)</td>
<td>−31% to 38%</td>
<td>8 (47%)</td>
<td>0–200% prolonged</td>
</tr>
<tr>
<td>Lowest postoperative</td>
<td>70–95 mm Hg</td>
<td>6 (19%)</td>
<td>12 (75%)</td>
<td>30–84 mm Hg</td>
</tr>
<tr>
<td>mean arterial pressure</td>
<td></td>
<td>48–119 mm Hg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PTT, partial thromboplastin time.

**Table 2.** Characterization and Comparison of Sterile Versus Septic Bile Peritonitis in 26 Dogs and Association with Mortality

<table>
<thead>
<tr>
<th>Bile peritonitis</th>
<th>Alive</th>
<th>Dead</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile (n = 15)</td>
<td>13</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Septic (n = 11)</td>
<td>5</td>
<td>6</td>
<td>$P = .038$</td>
</tr>
</tbody>
</table>
(3), sepsis (2), severe aspiration pneumonia (2), acute renal failure (1), pulmonary thromboembolism (1), seizures (1), and complications after cardiac resuscitation (1). Two dogs discharged from the hospital were returned within 4 days with no improvement in clinical signs; both were euthanized. Necropsy of these 2 dogs revealed 1 dog leaking bile from the cholecystectomy site and the other dog had dehiscence of the cholecystojjjunostomy site. Both dogs had diffuse peritonitis. Mean duration of hospitalization for surviving dogs was 6 ± 3 days.

**DISCUSSION**

The most common indication for biliary surgery in our study was necrotizing cholecystitis. Impaired cystic artery circulation by occlusion, bacterial infection or cystic duct obstruction from choleliths, neoplasia, or adjacent inflammatory processes may lead to cholecystitis.\(^1,5-10\) Mortality in our dogs with necrotizing cholecystitis was 25% compared with 39% in another report.\(^5\) Our highest perioperative mortality occurred in dogs with pancreatitis and/or associated periductal fibrosis or abscessation. Although 50% of dogs with pancreatitis died, no significant difference in mortality between these dogs and those with other causes was detected. The reason for high mortality in dogs with pancreatitis is unclear but may be associated with the effects of inflammatory mediator release rather than secondary effects of extrahepatic biliary tract obstruction.\(^5\)

Neoplasia has been reported as one of the most common causes of extrahepatic biliary tract obstruction in dogs,\(^1,4,6,11,12\); however, we did not observe this although there may have been selection bias associated because we excluded dogs euthanized before surgery. A presurgical diagnosis of neoplasia may have caused some owners to elect euthanasia before surgery.

Trauma appears to be an uncommon cause of biliary tract injury necessitating surgery and was associated with a good prognosis; all 4 dogs with traumatic biliary injuries survived. In this and other studies,\(^7,8,13-16\) the most frequent sites for traumatic injury were the common bile duct, the cystic duct, or hepatic ducts rather than the gallbladder. No underlying disease process was significantly associated with mortality despite considerable variation in incidence of perioperative death. This most likely reflects small case numbers precluding detection of statistically relevant differences (Type II error). It is also possible that systemic factors, like sepsis, renal dysfunction or coagulopathies that can be common to all of these conditions are more important predictors of short-term outcome than the underlying disease. It is likely that the underlying disease process is more predictive of long-term outcome in dogs that survive the perioperative period. We did not assess long-term outcome.

Bile peritonitis had occurred in 42% of our dogs. The most common causes were necrotizing cholecystitis, blunt trauma, and extrahepatic biliary tract obstruction. Previous reports\(^12,14\) indicate that trauma is the most common cause of biliary effusion in dogs but this and other reports,\(^3,5,16\) have identified necrotizing cholecystitis as a more prevalent cause. Bile induces a chemical peritonitis that remains fairly mild unless contaminated with bacteria,\(^1,17\) as occurred (aerobic and anaerobic bacteria) in our study. Mortality in our dogs with septic effusion (55%) was significantly higher than in those with a non-septic effusion (13%) and this corroborates outcomes in another report where 73% of dogs with septic effusions died compared with none that had nonseptic effusions.\(^3\)

In humans and dogs, a prolonged clinical course with bile peritonitis is common.\(^1,3,5,6,8,18\) Limited conclusions can be drawn from our study because many underlying diseases were present, of which some like those causing bile peritonitis, require prompt surgical intervention whereas others, like pancreatitis causing extrahepatic biliary tract obstruction, can often successfully be managed with medical treatment only.\(^6\)

Dogs in this study had an overall mortality rate of 28%. Other reported mortality rates for dogs that had biliary tract surgery range from 40% to 64%,\(^3,6,12,19\) with sepsis being the most common cause of death. Mortality rates of 8–30% have been reported for humans that had biliary tract surgery.\(^20\) Of 25 variables we assessed, presence of a septic bile peritonitis, increased serum creatinine concentration, prolonged PTT, and low postoperative mean arterial pressure were significantly associated with outcome. Previous veterinary studies have identified significant factors affecting survival in dogs that had surgery of the extrahepatic biliary tract as leukocytosis, circulating band neutrophils, and presence of bacteria in the biliary effusion.\(^3,4\) In humans, risk factors affecting mortality after extrahepatic biliary tract surgery include malignancy, age (> 60 years), fever, anemia, leukocytosis, azotemia, hypoalbuminemia, hyperbilirubinemia, and an increased ALP.\(^21\) As the number of risk factors present in a patient increases so does the correlation with mortality.\(^21\) Multivariate analysis was not performed in our study because of low numbers in the mortality outcome group.

One variable associated with a higher risk of mortality in our dogs was elevated preoperative serum creatinine concentration. Although there was no association between elevations in blood urea nitrogen (BUN) and mortality (\(P = 0.59\)), serum creatinine concentration tends to be a more sensitive predictor of glomerular filtration rate because it is produced at a constant daily rate and is less affected by dietary and other nonrenal factors. Preoperative elevations in serum creatinine concentrations may
have been either prerenal or renal in these dogs. Prerenal azotemia is most commonly associated with dehydration, especially in animals that are chronically anorexic, vomiting, or hypotensive.\textsuperscript{22} Renal azotemia may develop from shock, endotoxemia, and decreased renal blood flow leading to hypotensive ischemia. Humans,\textsuperscript{23} dogs,\textsuperscript{24} and rats\textsuperscript{25} with obstructive jaundice are at an increased risk of acute renal failure that develops because of bacterial endotoxemia. The mortality rate for humans with obstructive jaundice is significantly higher in patients with acute renal failure than in those without renal failure.\textsuperscript{23,26} In a rat model, the absence of bile salts in the small intestine enables the absorption of endotoxin.\textsuperscript{27,28} Gut-derived endotoxins are powerful renal vasoconstrictors and cause a decrease in intrarenal blood flow, a fall in glomerular filtration rate, and subsequent degeneration of the renal tubular epithelium.\textsuperscript{23,25,26} Preoperative urine specific gravity was not consistently measured in our dogs, so it is unclear whether the dogs with elevated serum creatinine concentration were actually in renal failure. However, because of the presence of obstructive jaundice and hypotension in many of these dogs, it is likely that a primary renal azotemia existed.

Two other factors statistically associated with outcome were immediate postoperative hypotension (LMAP (lowest mean arterial pressure)<70 mm Hg) and prolongation of PTT. Hypotension may have resulted from inadequate intravenous fluid resuscitation, prolonged anesthesia, or development of systemic inflammatory response syndrome (SIRS) and/or sepsis.\textsuperscript{23,24,29–33} Prolongation of PTT may have resulted from the inadequate absorption of vitamin K because of the absence of bile salts, liver dysfunction from underlying disease, or disseminated intravascular coagulation associated with SIRS/sepsis.\textsuperscript{1,4,23,31,34,35} In humans and rats, endotoxin produced changes in blood coagulation through effects of factors XI and XII,\textsuperscript{36} that would cause alterations in the intrinsic coagulation cascade and prolongation of PTT. Given the retrospective nature of our study, it was not possible to determine the cause(s) of increased preoperative creatinine concentration, prolonged PTT, or immediate postoperative hypotension in individual cases, or to causally link these factors to individual causes of death. However, it is interesting to evaluate these prognostic variables as a group in light of the other experimental and clinical studies of extrahepatic biliary disease. Whereas individual variables associated with mortality in our study have many potential causes, as a group they can all be reasonably linked to SIRS/sepsis. As discussed before, a likely stimulus for development of SIRS/sepsis in animals with decreased bile secretion is absorption of endotoxin.\textsuperscript{27,28} The presence of endotoxemia was not specifically evaluated; however, our results and the findings of previous experimental\textsuperscript{27} and human\textsuperscript{23,26,28} studies imply that endotoxin absorption may be an important factor in the pathophysiology of extrahepatic biliary disease in dogs.

The statistical association between presence of septic bile peritonitis, preoperative elevated creatinine concentration, immediate postoperative hypotension, and a poor outcome emphasizes the importance of adequate fluid resuscitation, maintaining adequate tissue perfusion, and careful monitoring of tissue perfusion indicators, including blood pressure, arterial and mixed venous blood gases, lactate, and urine output in dogs with extrahepatic biliary disease. These variables can be used in a clinical setting to better evaluate the mortality risk for each patient during the perioperative period.

REFERENCES