A Multivariate Analysis of Preoperative Risk Factors in Patients with Common Bile Duct Stones

Implications for Treatment

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A multivariate analysis of 30 preoperative risk factors was undertaken in 248 patients who underwent surgery alone for common bile duct (CBD) stones and in 190 patients who had endoscopic sphincterotomy (ES), 77 of whom subsequently also had surgery. Independently significant risk factors in those undergoing surgery were the serum bilirubin level, the use of preoperative ES, and the presence of medical risk factors; in patients undergoing ES, only the serum bilirubin and albumin, but not medical risk factors, were of independent significance. The major implications of this study are, first, that high-risk patients should be treated by ES without subsequent surgery, and second, that "fit patients should be treated by surgery alone *without* routine preoperative ES.

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ENDOSCOPIC SPHINCTEROTOMY (ES) with active stone extraction is being used increasingly in the management of patients with common bile duct (CBD) stones.[1-3] Acceptable bile duct clearance rates are now considered to be 90% or more,[1-4] and these are comparable to those achieved by surgical means.[5-7] A 10–15% complication rate and a mortality of approximately 3% or less for ES[8] are judged to be as good as or superior to surgery.[9,10] ES has become established as the treatment of choice in patients who have had a previous cholecystectomy either remotely[1,8,9] or in the early postoperative period.[1,11]

More recently, increasing use of ES has been recommended for treatment of patients with gallbladders *in situ* who are at increased surgical risk.[2,9,12] In relatively fit patients, use of ES may be followed by elective cholecystectomy;[12] in the elderly and/or high-risk patients, the gallbladder need not be removed, because only some 10% of these patients develop symptoms from gallbladder stones.[1-3] Surprisingly, preoperative risk factors for surgical treatment of CBD stones are poorly described and have been defined only through the use of *univariate* analysis.[13] Two studies have used multivariate analysis to assess risk factors in jaundiced patients, but these series were largely composed of patients with malignant disease.[14,15] Moreover, there have been no studies that have assessed risk factors in patients undergoing ES.

We have therefore determined independent risk factors for patients with CBD stones undergoing surgery with or without preoperative ES and also for those patients undergoing ES as the only intended form of treatment.

Patients and Methods

The study population consisted of all patients undergoing operative exploration of the CBD and/or ES for CBD stones during a consecutive 5-year period (1981–1985, inclusive). In just more than half of the cases the data was collected prospectively. In order to reduce bias, included in the analysis were all similar cases admitted during the same period. These patients were identified by use of the Hospital Activity Analysis diagnostic and operation codes and were cross-checked with those patients who had undergone an endoscopic retrograde cholangiopancreatography (ERCP)((all of whom were entered prospectively into a data base) and/or had been entered into a prospective surgical audit.

Ten admission clinical factors and 14 admission hematologic/biochemical variables were entered into a proforma. Medical risk factors (MRF) were also recorded; these were defined as any cardiovascular or respiratory condition requiring long-term drug therapy, diabetes mellitus requiring oral hypoglycemics or insulin, any medical condition requiring long-term steroids, and any

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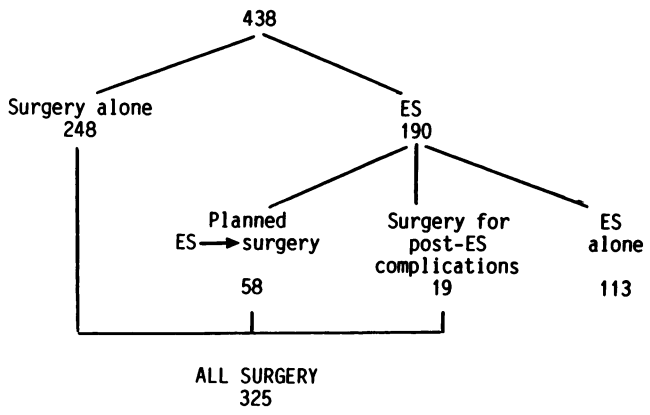

FIG. 1. Treatment of the 438 patients in the study: surgery alone (n = 248), ES alone (n = 113) and ES followed by surgery (n = 77).

major psychiatric disorder (psychosis or dementia) or central nervous system disturbance (hemiplegia, multiple sclerosis). Each MRF was given a score of "one" without any attempt at weighting.

The procedures (surgical and/or endoscopic), findings at surgery and/or ERCP, and the postprocedural outcome were recorded. Complications were qualified by minor complications (non-life-threatening) and major complications (life-threatening).

All the information was coded and entered into a mainframe computer. Univariate analysis was performed using the X^2 test and analysis of variance. Multivariate stepwise logistic regression analysis was then performed to identify independently significant factors for use in predicting complications.[16] Significance was taken as $p < 0.05$.

Results

Four hundred thirty-eight patients in all were identified, and of these, 248 underwent surgery alone. The other 190 patients had ES; in 132 cases this was intended as the only procedure to be undertaken; in the remaining 58 cases, it was followed by surgery as part of a deliberate treatment policy. Nineteen of the former 132 patients, however, also went on to have surgery either because of failed ES and/or failed stone extraction or because of post-ES complications. Thus, overall, 325 patients had surgery, 77 of whom underwent (attempted) preoperative ES (Fig. 1).

TABLE 1. *Postoperative Complications in the 325 Patients who Underwent Surgery*

Complication	No. of Patients	%
Wound infection	40	12.3
Respiratory failure	25	7.7
Biliary leak	20	6.2
Hemorrhage	10	3.1
Intra-abdominal abscess	10	3.1
Septicemia	6	1.8
Bacteremia	6	1.8
Renal failure	4	1.2
Pulmonary embolus	3	0.9
Acute pancreatitis	3	0.9
Cerebrovascular accident	2	0.6
Deaths	14	4.3
Total number of patients with complications	83	25.5

TABLE 2. *Post-ES Complications in the 190 Patients who Underwent Attempted ES*

Complication	No. of Patients	%
Acute cholangitis	15	7.9
Hemorrhage	5	2.6
Septicemia	4	2.1
Acute pancreatitis	3	1.6
Empyema of gallbladder	2	1.1
Gastric erosions	2	1.1
Cardiac failure	2	1.1
Perforation	1	0.5
Deaths	11	5.8
Total number of patients with complications	32	16.8

The complications that occurred after surgery are shown in Table 1. There was no relationship between the types of operation, grade of surgeon, and postoperative outcome. The complications that occurred after ES are shown in Table 2. The clinical and technical details of the procedures undertaken in these 438 patients have been fully described and discussed elsewhere.[17]

Univariate Analysis

The results of univariate analysis of postprocedural complications in relation to clinical factors and hematologic/biochemical variables are shown in Tables 3 and 4, respectively. It is important to note that only postoperative sequelae are considered in the analysis of surgical patients, even if the patient had had a complication after ES, before surgery; similarly, only postprocedural sequelae are considered in the analysis of ES patients, irrespective of the outcome after surgery, if surgery was undertaken.

Eighty-three patients had complications after surgery (n = 325); 51 of these had minor complications, and 32 had major complications. There were therefore sufficient numbers to consider the various factors in relation to major or minor complications separately. The results showed that the presence of clinical jaundice and medical risk factors, decreased levels of serum urea and creatinine, and increased levels of serum bilirubin were all significantly associated with major as well as minor complications (Tables 3 and 4). All but four of the 32 patients who had complications after ES (n = 190) had major complications, so that a similar analysis was not possible.

Univariate analysis showed considerable differences

TABLE 3. *Results of Univariate Analysis of Clinical Factors in Relation to Complications that Occur After Surgery (n = 325) or ES (n = 190)*

	Surgery			Endoscopic Sphincterotomy		
	Complications n = 83	No Complications n = 242	p	Complications n = 32	No Complications n = 158	p
*Age (years)	62 (20–89)	57 (18–87)	0.029	70 (20–92)	70 (22–89)	NS
Females	45 (54%)	156 (64%)	NS	16 (50%)	99 (63%)	NS
Preoperative ES	28 (34%)	49 (20%)	0.0128			
Jaundice	51 (61%)	90 (37%)	<0.001†	27 (84%)	108 (68%)	0.069
Temperature > 38 C	14 (17%)	28 (12%)	NS	11 (34%)	32 (20%)	0.082
Acute cholangitis	11 (13%)	19 (8%)	NS	11 (34%)	17 (11%)	<0.001
Acute pancreatitis	6 (7%)	8 (3%)	NS	2 (6%)	20 (13%)	NS
*Medical risk factors (mean score)	0.66 (0–4)	0.38 (0–4)	0.004†	1.9 (0–4)	1.8 (0–5)	NS
Presence of medical risk factors	36 (43%)	65 (27%)	0.005†	22 (69%)	112 (71%)	NS

* Mean values (range).
† Factors also significant if minor and major complications considered individually: jaundice ($p < 0.001$), medical risk factor mean scores ($p = 0.008$), presence of medical risk factors ($p < 0.01$).

between the group of patients that underwent surgery alone (n = 248) and the group that underwent ES (n = 190). Patients in the latter group were older ($p < 0.001$), there was a greater number of patients with clinical jaundice ($p < 0.001$), temperature > 38 C ($p < 0.001$) and acute cholangitis ($p = 0.011$). They had higher serum levels of urea ($p < 0.001$), creatinine ($p = 0.035$), alkaline phosphatase ($p < 0.001$), γ-glutamyl transpeptidase ($p < 0.001$), alanine transaminase ($p = 0.073$), and bilirubin ($p = 0.031$). The hematocrit was lower ($p < 0.001$), as was the serum albumin ($p < 0.001$), and they also had more MRFs ($p < 0.001$). There was no difference in relation to the sex distribution, the proportion with acute pancreatitis, the hemoglobin, white blood cell count, and serum total protein levels.

Considering all 438 patients together, eight factors were found to be significantly different in relation to increased postprocedural/postoperative complications. These were sex (there were more males, $p = 0.031$); the greater proportion of patients with jaundice ($p = 0.003$); temperature > 38 C ($p = 0.047$); acute cholangitis ($p < 0.001$); higher levels of serum urea ($p < 0.001$), creatinine ($p < 0.005$), and bilirubin ($p < 0.001$); and a lower serum albumin ($p = 0.007$).

Multivariate Analysis

Multivariate analysis showed that, in the surgical patients (n = 325), only three factors had independent significance in terms of predicting complications: the serum bilirubin level (BIL), the presence of MRFs, and whether or not ES had been attempted. The probability of developing complications (p) was calculated by the following:

$$\text{logit } p = 0.51\,(\text{MRF}) + 0.533\,(\text{ES}) + 0.0003\,(\text{BIL}) - 1.627$$

where presence of one or more MRF = 1, and absence of MRF = 0; preoperative ES = 1, and ES not attempted = 0; and the bilirubin is expressed as mmol/L. Examples of the probability of complications using various values for bilirubin, with or without MRF and/or ES, are given in Table 5. The use of an MRF score in cases with more

TABLE 4. *Results of Univariate Analysis of Hematological and Biochemical Variables in Relation to Complications After Surgery (n = 325) or Endoscopic Sphincterotomy (n = 190)*

	Surgery			ES		
	Complications n = 83	No Complications n = 242	p	Complications n = 32	No Complications n = 158	p
Hemoglobin (g/dl)	13.6 (10.3–17.2)	13.8 (9.1–17.5)	NS	13.3 (7.5–16.1)	13.5 (4.4–16.8)	NS
Hematocrit (%)	40.8 (31.7–51.4)	41.1 (28.8–51.5)	NS	39.1 (22.5–47.4)	40.4 (28.2–50.6)	NS
White blood cell count ($\times 10^9$/l)	9.3 (3.3–26.9)	8.6 (2.5–21.8)	NS	11.3 (4.7–35.3)	9.9 (1.2–40.6)	NS
Urea (mmol/l)	5.8 (2.1–25.7)	5.0 (1.9–23.9)	0.091*	9.4 (2.0–28.7)	5.9 (1.9–23.9)	<0.001
Creatinine (μmol/l)	97 (45–377)	86 (40–280)	0.072*	115 (44–304)	92 (10–280)	0.014
Total proteins (g/l)	66.8 (46–82)	66.5 (48–85)	NS	62.3 (44–77)	65.8 (40–82)	0.035
Albumin (g/l)	38.0 (24–48)	39.6 (22–52)	0.040	33.6 (24–42)	37.1 (24–48)	0.006
Alkaline phosphatase (iu/l)	420 (70–1755)	335 (20–2629)	0.084	532 (89–1560)	493 (62–3074)	NS
γ-glutamyl transpeptidase (iu/l)	351 (14–1130)	268 (5–1914)	0.062	375 (18–1926)	376 (10–1213)	NS
Alanine transaminase (iu/l)	180 (8–1134)	148 (1–1012)	NS	141 (12–413)	182 (4–1134)	NS
Bilirubin (μmol/l)	118 (7–841)	71 (3–474)	<0.001*	156 (14–683)	90 (3–709)	0.003

* Factors significant if minor and major complications considered individually: urea ($p = 0.0151$), creatinine ($p < 0.001$), bilirubin ($p = 0.001$).

TABLE 5. *Probability of Complications Developing After Surgery (n = 325) Given Various Values of Bilirubin with or without MRF/Preoperative ES*

MRF-ES	Serum Bilirubin (μmol/l) 25	100	200	300	400
MRF = 0 ES = 0	0.174	0.206	0.256	0.313	0.376
MRF = 1 ES = 0	0.260	0.302	0.364	0.431	0.501
MRF = 0 ES = 1	0.264	0.307	0.370	0.437	0.507
MRF = 1 ES = 1	0.374	0.425	0.494	0.564	0.631

than one MRF did not improve the predictability of the model. Categorization of ES into failure or success, with or without complications, also did not improve the predictability of the model. The presence of MRFs and preoperative ES had a similar power in this model.

In patients undergoing ES (n = 190), only two factors were of independent significance in predicting post-ES complications: the BIL and the serum albumin (ALB). The probability of developing complications (p) was calculated by the following:

$$\text{logit } p = 0.004\ (\text{BIL}) - 0.107\ (\text{ALB}) + 1.46$$

where the bilirubin is expressed in mmol/l and albumin in g/l. Examples of the probability of complications using various values for bilirubin and albumin are given in Table 6.

Considering all 438 patients together, there were only two variables that predicted postprocedural/postoperative complications: the serum levels of bilirubin and urea. In this instance, the probability of developing postsurgical or post-ES complications was calculated by the following:

$$\text{logit } p = 0.098\ (\text{UREA}) + 0.0032\ (\text{BIL}) - 2.330$$

where urea is expressed in mmol/l, and bilirubin in mmol/l.

Discussion

This is the first study that has assessed independent preoperative/postprocedural risk factors in a substantial group of patients with CBD stones with respect either to surgery alone, or ES alone, or both. There are three important conclusions: 1) the serum bilirubin was the single most important predictor of postprocedural outcome, not only in relation to surgery, but also in relation to ES; 2) preoperative ES was associated with a higher postoperative complication rate (irrespective of post-ES complications); and 3) the presence of medical risk factors (MRF) was a determinant of postoperative outcome *but not of outcome after ES.*

TABLE 6. *Probability of Complications Developing After ES (n = 190) Given Various Values of Serum Albumin and Bilirubin*

Serum Albumin (g/l)	Serum Bilirubin (μmol/l) 25	100	200	300	400
36	0.091	0.116	0.157	0.211	0.276
32	0.133	0.167	0.223	0.291	0.370
28	0.191	0.235	0.306	0.386	0.474
24	0.265	0.321	0.403	0.490	0.580

The actual serum level of bilirubin was important in predicting postoperative/postprocedural outcome. The degree of hyperbilirubinemia reflects the degree of liver dysfunction affecting both nutrition and reticuloendothelial clearance[18] and is consistent with our findings. Blamey et al.,[15] in a surgical study of 186 patients (64 with stones, 72 with malignancy, 50 with other conditions) found that bilirubin, albumin, and creatinine were all independently significant. In the present study, we found that in addition to bilirubin, only albumin was independently significant in patients undergoing ES. In patients undergoing surgery, albumin (as well as other factors) lost independent significance when medical risk factors and preoperative ES were considered along with bilirubin; removal of ES as a factor from the regression equation still excluded albumin as an independent predictor because of the overriding significance of MRF and bilirubin. Previous authors have not included concomitant disease in assessing postoperative risk in biliary disease, although it would seem logical because it is probably the most important factor taken into account when making clinical decisions.

The finding of an increased postoperative complication rate in patients who also had ES before surgery was surprising. Although patients undergoing ES had more adverse clinical and biochemical factors compared with the patients who had surgery alone, these factors were accounted for by the multivariate analysis. There appear to be two factors contributing to the adverse postoperative affects of preoperative ES. First, the development of complications attributable to ES (*e.g.*, bleeding, cholangitis) probably compromised the overall status of these patients, thereby increasing the likelihood of postoperative complications. Second, ES results in an increased incidence of infection in the biliary tree,[19,20] irrespective of complete clearance of CBD stones.

The implications of these findings are as follows: 1) patients should not be subjected to ES unless it is intended to be the only form of treatment; and 2) patients who develop complications post-ES should be considered for further nonoperative means of treatment when possible; the latter includes percutaneous gallbladder drainage of pus followed by gallstone dissolution[21,22] and the routine use of naso-biliary catheters or wide bore endoprostheses when CBD stone clearance has been incomplete.[23] The

wider availability of extracorporeal shock wave lithotripsy for gallstones, either in the gallbladder or CBD,[24] should increase the therapeutic options.

MRFs are known to be associated with increased postoperative complications.[25] Although biliary surgery often involves elderly patients with additional medical problems, they have not been previously incorporated into multivariate analyses. The findings of the present investigation should prompt similar studies in other areas of surgery that carry a high operative mortality.

In contrast to surgery, there was a lack of any correlation between outcome after ES and the presence of MRF. This supports the view that patients with medical risk factors should be strongly considered for endoscopic treatment alone rather than for surgery.[2,9,26] This does not, however, indicate that "fit" elderly patients should not also undergo operation. Surgery offers the best option in that it not only removes the CBD stones, but also eliminates the possibility of long-term gallbladder complications that occur after ES alone in approximately 10% of patients.[1-3,26]

Finally, the probability tables of postprocedural risk determined by this study should enable an accurate stratification of patients undergoing various treatment strategies in future prospective studies.

In conclusion, this study has provided a rationale for the treatment of high-risk cases by ES alone and should encourage the current trend. On the other hand, patients who are fit enough for surgery should not undergo routine preoperative ES. There are, however, some exceptions to this, including patients with severe acute pancreatitis and/or acute cholangitis.[27-29] Although preoperative ES has recently been recommended for high-risk patients,[30] they are probably best treated by ES alone.

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