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DELAYED REFERRAL TO SPECIALIST CENTRE INCREASES MORBIDITY IN PATIENTS WITH BILE DUCT INJURY (BDI) AFTER LAPAROSCOPIC CHOLECYSTECTOMY (LC)

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Abbreviations used

BDI- Bile duct injury
LC- Laparoscopic cholecystectomy
ERG- Early referral group
LRG- Late referral group
HPB- Hepato-pancreato-biliary
LFTs- Liver function tests
MRI- Magnetic resonance imaging
ERCP- Endoscopic retrograde cholangio pancreatography
OTC- On table cholangiogram
RHA- Right hepatic artery

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ABSTRACT

Background

There is still a debate regarding the optimal management of bile duct injury following cholecystectomy. Our aim was to ascertain if delayed referral influenced clinical outcomes for patients with BDI treated in our institution.

Materials and Methods

We interrogated a prospectively maintained database, including all patients with BDI (Bismuth and Strasberg classifications) post LC managed in our unit from 2000-2014. Referrals were arbitrarily defined as early (< 96 hours from the injury) and delayed (> 96 hours).

Results

68 patients with BDI were managed. Patient demographics, referral time, level of injury and morbidity data was collected. 50 patients (77%) required a surgical bile duct reconstruction. The *Early referral Group* included 33 patients (52.4%) and *Delayed referral group* 30 (47.6%).

The patients referred late had a significantly high incidence of right hepatic artery injury (23% vs. 3%) and the overall number of complications (0.0001). The average number of surgical interventions (2.5 vs 1.8, $p<0.05$) and invasive procedures (4 vs. 2.5, $p< 0.05$) per patient was high in the late referral group.

There was significant difference in the interval between BDI-to-reconstruction (median 3 vs. median 88 days, $p< 0.05$) and referral-to-hospital discharge (median 9 vs. median days 59, $p< 0.05$).

On multivariate analysis only delayed referral (OR 7.58, 95% CI 2.1-26.6) and Strasberg-E injuries (OR 4.86, 95% CI 1.1-20.9) were significant.

Conclusion

A late referral was associated with a higher incidence of post-treatment complications, greater need for invasive procedures and a longer recovery period. These observations support the need for early patient transfer to a tertiary institution following BDI.

INTRODUCTION

Bile duct injury (BDI) is a recognized complication following a cholecystectomy and has been associated with high morbidity rates, poor survival and impaired quality of life (1, 2) (3).

The incidence of BDI increased with the introduction of the laparoscopy as a preferred approach for cholecystectomy (1, 2, 4) (5) (6).

According to large series, mainly from US, the prevalence is around 0.3-0.5% with a potential 400 BDIs per year (1, 4, 7, 8). It is estimated that close to a 70,000 laparoscopic cholecystectomies (LCs) are performed every year in the UK with a prevalence of BDI around 0.4-0.9%.

Several publications have addressed the ideal manner to manage BDIs and it is generally accepted that the best outcome following a BDI is achieved in tertiary centres with HPB expertise (2, 8, 9) (10, 11). In addition, a number of papers have compared the results in patients with BDI undergoing early or late repair although no with no clear differences were shown between both the groups (1, 12, 13).

However, there is a scarce data analysing the outcomes of patients based on the timing of referral to a specialist tertiary HPB centre. Our study aimed to assess the impact of the referral timing (early vs. late) on postoperative and long term outcomes after BDI.

MATERIAL AND METHODS

Data

A retrospective analysis of all patients managed at St James's University Hospital (SJUH) with BDI post cholecystectomy from January 2000 to December 2014 was performed. Patients were identified from a prospectively maintained database.

Data obtained prior to referral

The data collected included patient demographics, details concerning the initial cholecystectomy, the use of intraoperative cholangiogram and whether the BDI was recognized during the cholecystectomy or not. The length of time elapsed from injury to diagnosis of BDI was obtained, as well as subsequent interventions performed at the local hospital prior to the patient's transfer.

Data obtained following referral

The date on which the referral centre contacted us for the first time was recorded as the referral date regardless whether the patient was physically transferred on that day or later due to bed availability.

The length of time from the cholecystectomy to the referral was obtained. For further data analysis, we considered 'early referral' when it occurred within the 96 hours from the BDI and 'delayed referral' if it was later than 96 hours (12-15).

The extent of the injury was determined according to Bismuth (16) and Strasberg (17) classifications.

All invasive procedures required in our hospital were recorded, including radiological and surgical. If a surgical reconstruction was needed, technique and operative findings were also described. Critical care requirement and length of stay in hospital were recorded. BDI index-treatment was defined as the treatment provided in our hospital intended to repair the BDI.

Follow up

Patients were routinely followed up in our outpatient department. Postoperative complications were recorded for each patient and defined as any adverse event developed after admission in our unit, according the Clavien-Dindo classification (18). We also divided all these complications into 'Early' (events requiring treatment or readmission within 30 days after the BDI index-treatment) and 'Late' complications.

Bile leak was defined as bile contained in surgical drains after the first postoperative day or a leak demonstrated by cholangiography.

Cholangitis was defined by the presence of fever and worsening liver function tests (with/ without abdominal pain) requiring antibiotic treatment. Acute cholangitis was diagnosed during the initial admission and recurrent following discharge.

Biliary stricture was defined by a progressive cholestatic pattern in LFT's with radiological evidence on MRI/ MRCP. Reoperation was any surgical intervention required after index BDI treatment.

Chronic pain was considered as a complication when the patient required referral to the Pain team during the follow up for further management.

The time intervals from the BDI to the BDI index-treatment, from the referral to the BDI index-treatment and from referral to discharge from our hospitalization, were also calculated.

Statistical analysis

Data analysis was performed with SPSS softwareV.20 (SPSS, Chicago, IL). Comparison between groups was performed with Student-t and X^2-test when appropriate. For categorical variables, Fisher's exact test was used when a table had a cell with and expected frequency less than 5.

By defining "major complication" (including complications Clavien-Dindo 2 or more developed after admission in our unit) as a dependent variable univariate (yes/no) a multivariate analysis (linear regression) was performed. Statistical significance was accepted if $p<0.05$.

RESULTS

Overall series

Sixty-eight patients were managed for BDI post cholecystectomy during the studied period (2000-2014). The mean age was 54 (range 17-86) and 71% of the patients were women. Five patients were finally excluded from the analysis as they had been referred several years (median of 5 years, mainly anastomotic strictures) after the initial BDI and had been initially managed in other centers.

At the referring center (before referral)

Patient demographics, initial management at local hospital and associated injuries are detailed in Table 1.

The initial cholecystectomy approach was laparoscopic in 58.7% (n=37), laparoscopic converted to open in 38.1% (n=24) and open in 3.2% (n=2).

On table cholangiogram (OTC) was performed only in 6 patients (9.5%) after BDI was suspected. The BDI was identified in 23 cases (36.5%) by the operating surgeon during the cholecystectomy. Based on imaging and according to Bismuth classification, 54% of the patients had a Grade I-II injury (injuries not involving the hepatic ducts confluence) and 46% were higher injuries involving the confluence (Grade III-IV).

According to Strasberg classification, 66.7% of the patients presented with class E lesions (complete transection of the bile duct). In 8 patients (12.7%), the Right Hepatic Artery was injured along with the bile duct.

In our center (following referral): BDI index-treatment (Table 2)

55 out of 63 patients (87%) required a surgical intervention: 5 surgical drainage (including one case of completion cholecystectomy) and 50 bile duct surgical repair (79%). This included primary repair and T tube insertion (3), hepaticojejunostomy (37), hepaticojejunostomy plus hepatectomy (5) and revision of the initial hepaticojejunostomy (5). Only 8 out of 63 patients did not undergo surgery and were managed radiologically (8 ERCP).

Delayed vs. Early referral

Table 3 summarises the clinical outcomes based upon the referral timing and identified after BDI index-treatment. When a patient developed more than one complication, all were recorded.

A total of 53% patients (33) were classified as early referral or ERG (less than 96 hours after injury) whilst 47% (30) were in the delayed referral group or DRG (longer than 96 hours).

There were no significant differences in age, gender, selected approach for the initial cholecystectomy, percentage of attempted repair at local institution or Bismuth classification between the two groups.

Grade E Strasberg lesions with associated right hepatic artery injury were significantly more prevalent among the DRG suggesting a more complex diagnosis in these patients (p=0.032).

The number of patients developing complications was significantly higher in the DRG (89%) when compared to the ERG (36%,p=0.0001). When we looked separately at the incidence of early and late complications, the DRG again experienced a higher incidence of both.

Patients with a delayed referral required overall more episodes of readmissions (70% vs. 21%, p= 0.0001) as well as presented with more episodes of recurrent cholangitis (p=0.017).

However, incidence of bile leak, bile duct stricture and chronic pain were similar between groups.

The ratio of procedures required per patient (surgical or radiological) in the ERG was 2.5 vs. 4 for the DRG (p=0.01). The ratio of surgical interventions per patient in the early group was 1.8 vs. 2.5 (p= 0.025)

Univariate and multivariate analysis was performed with "Major Complication developed after BDI index-treatment" in our centre as a dependent variable. Results are shown in table 3.

Patients requiring surgical reconstruction after referral, delayed referral and Strasberg E classification were significant in the univariate analysis.

The multivariate analysis identified 2 independent prognostic factors significantly associated with higher risk of complications: delayed referral with OR=7.58 (CI, 2.15-26.6) and Strasberg classification E with OR of 4.86 (CI, 1.13-20.9).

DISCUSSION

The present study is aimed to determine if the referral pattern influences the outcomes of patients after BDI and in particular if a delayed referral can be an independent factor for increased morbidity.

Following the recognition of a BDI, providing prompt repair by specialist surgeon achieves the optimal results. Several authors have tried to define different time limits to consider an early surgical repair, varying significantly from 2 days to 6 weeks (1, 2, 4).

Some recent publications have strongly suggested that surgical reconstruction within the first 96 hours after BDI is safe and provides good results (1, 12). Accordingly, to validate our hypothesis we have adopted this period of time to define an early referral and therefore to stratify our cohort of patients.

We present our series with 63 patients that sustained a BDI, were treated in our centre with substantial long follow up (median of 707 days). The vast majority of them were sustained after a laparoscopic cholecystectomy and only 36% were recognized intraoperatively. Of concern, 12.7% of patients had a right hepatic artery injury in addition. Up to 28% of patients had a local intervention to repair the BDI, namely T-tube insertion or hepaticojejunostomy. The overall median time to referral was 4 days. Following transfer to our center, 87% required surgery (index BDI treatment) and 79% a surgical procedure to restore the BD continuity. In other words, BDI equaled to a re-intervention almost invariably.

Further analysis was stratified according the referral pattern, early vs. later (more than 96h). As a consequence of this, we created an ERG (30 patients) with a median time to referral of 1 days and a DRG (33 patients) with a median of 17 days. Preoperative

demographics were similar and the degree of injury was similar when using Bismuth classification. However, the incidence of Strassberg-E injuries was higher amongst late referrals as well as the number of patients with RHA injury (E1). This might constitute a bias as reflected by more patients treated conservatively (ERCP or laparoscopic wash out only) in the ERG (33% vs.6%).

There is increasing evidence of the use of ERCP in minor leak following BDI. In our series only 11 out of 63 (17%) patients needed ERCP at our institute as 21 patients (33%) had Strasberg A to D injury and 42 patients (66%) had Strasberg E injury requiring surgical treatment. This is a reflection of the fact that minor BDI were treated at local hospital and the severe injuries were referred to our specialist HPB centre.

In our series we had information regarding the severity of original disease in 26 out of 63 patients (41%). 19 out of 26 patients (73%) had complicated gall stone disease (including cholecystitis, empyema, Mirizzi disease, CBD stone, cholecysto-colic fistula), thus indicating a high incidence of BDI in complicated gall stone disease. We feel this supports the view that such cases should be referred early to specialist HPB centre for management.

The most significant implication of a late referral was an obvious delay in providing the BDI index-treatment, 3 days for the ERG versus 88 days for the DRG (median). Although this may reflect a direct consequence of our stratification there was also (1) evidence of an increased morbidity within the DRG and (2) a significantly longer referral-to-discharge time (9 vs. 59 median days). The number of patients in the DRG

that experienced complications after their BDI index-treatment was significantly higher (89%), suggesting a more protracted recovery and/or a major trauma. In addition, the percentage of early postoperative complications was also greater when a delayed referral was made and that translated into more procedures per patient required following the BDI (4 vs. 2.5). Although these results might be questioned by the volume and design of the study, it seems reasonable to assume that a late referral carried a significantly greater number of morbid events. That might have been due to a missed opportunity to promptly repair the BDI in a more favorable environment (no sepsis, less inflammation, lesser interference from the referring hospital) (1, 2, 14, 19). Moreover there was a higher proportion of Strasberg E and E1 injuries in the DRG due to a failure to recognize these injuries intraoperatively. There is little doubt that different outcomes when comparing ERG and DRG are multifactorial as suggested by the multivariate analysis. In our experience, the only two predictor factors for "developing a major complication" where the delayed referral (HR of 7.5) and the Strasberg E classification (HR of 4.8). In any case, we speculate that early referral could 1) allow for a prompt repair in a specialized center when appropriate or 2) facilitate identification of severe injuries and again better management in a tertiary hospital. Those are more likely to require a deferred approach and the tertiary centre provides not only the potential of surgical reconstruction but a better BDI characterization, therapeutic planning, experienced interventional radiology and endoscopy team, to be able to design the optimal treatment for each patient.

CONCLUSION

Unfortunately, BDI following cholecystectomy remains a problem. Despite all the evidence favoring the treatment of BDI in a specialized multidisciplinary centre, there is still a wide variability in referral patterns. A significant number of BDI are still referred late with multiple previous interventions at the local center and often underestimating the magnitude of the trauma.

Based on our experience but also supported by large volume center publications (5, 13, 14), early referral is possibly one of the main predictor variables when treating a bile duct injury. When a BDI is suspected, early referral provides the best possible outcome and is strongly encouraged.

List of abbreviations

BDI- Bile duct injury

LC- Laparoscopic cholecystectomy

ERG- Early referral group

LRG- Late referral group

HPB- Hepato-pancreato-biliary

LFTs- Live function tests

MRI- Magnetic resonance imaging

ERCP- Endoscopic retrograde cholangio pancreatography

OTC- On table cholangiogram

RHA- Right hepatic artery

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REFERENCES

1. Boerma D, Rauws EA, Keulemans YC et al. Impaired quality of life 5 years after bile duct injury during laparoscopic cholecystectomy: a prospective analysis. *Ann Surg* 2001;234:750-757.
2. Flum DR, Cheadle A, Prela C, Dellinger EP, Chan L. Bile duct injury during cholecystectomy and survival in medicare beneficiaries. *JAMA* 2003;290:2168-2173.
3. Yang WL, Zhang DW, Zhang XC. Clinical analysis of patients with iatrogenic bile duct injury. *Hepatobiliary Pancreat Dis Int* 2006;5:283-285.
4. Adamsen S, Hansen OH, Funch-Jensen P, Schulze S, Stage JG, Wara P. Bile duct injury during laparoscopic cholecystectomy: a prospective nationwide series. *J Am Coll Surg* 1997;184:571-578.
5. Stewart L, Way LW. Bile duct injuries during laparoscopic cholecystectomy. Factors that influence the results of treatment. *Arch Surg* 1995;130:1123-8; discussion 1129.
6. Fletcher DR, Hobbs MS, Tan P et al. Complications of cholecystectomy: risks of the laparoscopic approach and protective effects of operative cholangiography: a population-based study. *Ann Surg* 1999;229:449-457.
7. Sinha S, Hofman D, Stoker DL et al. Epidemiological study of provision of cholecystectomy in England from 2000 to 2009: retrospective analysis of Hospital Episode Statistics. *Surg Endosc* 2013;27:162-175.
8. Archer SB, Brown DW, Smith CD, Branum GD, Hunter JG. Bile duct injury during laparoscopic cholecystectomy: results of a national survey. *Ann Surg* 2001;234:549-58; discussion 558-9.

9. Melton GB, Lillemoe KD, Cameron JL, Sauter PA, Coleman J, Yeo CJ. Major bile duct injuries associated with laparoscopic cholecystectomy: effect of surgical repair on quality of life. *Ann Surg* 2002;235:888-895.

10. Sicklick JK, Camp MS, Lillemoe KD et al. Surgical management of bile duct injuries sustained during laparoscopic cholecystectomy: perioperative results in 200 patients. *Ann Surg* 2005;241:786-92; discussion 793-5.

11. Gouma DJ, Go PM. Bile duct injury during laparoscopic and conventional cholecystectomy. *J Am Coll Surg* 1994;178:229-233.

12. Felekouras E, Petrou A, Neofytou K et al. Early or Delayed Intervention for Bile Duct Injuries following Laparoscopic Cholecystectomy? A Dilemma Looking for an Answer. *Gastroenterol Res Pract* 2015;2015:104235.

13. Fischer CP, Fahy BN, Aloia TA, Bass BL, Gaber AO, Ghobrial RM. Timing of referral impacts surgical outcomes in patients undergoing repair of bile duct injuries. *HPB (Oxford)* 2009;11:32-37.

14. de Reuver PR, Grossmann I, Busch OR, Obertop H, van Gulik TM, Gouma DJ. Referral pattern and timing of repair are risk factors for complications after reconstructive surgery for bile duct injury. *Ann Surg* 2007;245:763-770.

15. Schmidt SC, Langrehr JM, Hintze RE, Neuhaus P. Long-term results and risk factors influencing outcome of major bile duct injuries following cholecystectomy. *Br J Surg* 2005;92:76-82.

16. Bismuth H, Majno PE. Biliary strictures: classification based on the principles of surgical treatment. *World J Surg* 2001;25:1241-1244.

17. Strasberg SM, Hertl M, Soper NJ. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. *J Am Coll Surg* 1995;180:101-125.

18. Clavien PA, Barkun J, de Oliveira ML et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250:187-196.

19. Stewart L. Iatrogenic biliary injuries: identification, classification, and management. *Surg Clin North Am* 2014;94:297-310.

Table I. Characteristics before referral

	Number (n=63)	%
Initial operation		
Laparoscopic	37	58.7
Laparoscopic converted to open	24	38.1
Open	2	3.2
Intraoperative recognition of injury	23	36.5
OTC	6	9.5
RHA injury	8	12.7
Immediate intervention (prior transfer)		
Wash/Drain-initial cholecystectomy	21	33.3
Primary repair/T-tube	9	14.3
ERCP/stent	18	28.6
PTC/percutaneous drain	2	3.2
Hepatico-jejunostomy	9	14.3
Referral time (days)		
Mean	75.71 (0-1825)	
Median	4	
Bismuth (level of injury)		
I-II	34	54.0
III-IV	29	46.0

Strasberg (type + level of injury)		
A-D	21	33.3
E (complete transection)	42	66.7

Table II. Following referral

	Number (n=63)	%
Pre-op procedure (SJUH)		
ERCP/Stent	11	17.5
PTC	2	3.2
Percutaneous drainage	6	9.5
None	41	65.1
BDI Index-Treatment	55	87%
Wash/Drainage	4	7
Primary repair/T-tube	3	5
Hepatico-jejunostomy	37	67
Hepatico-jejunostomy + liver resection	5	9
Re-do hepatico-jejunostomy	5	9
Completion cholecystectomy/drainage	1	2

Table III: Clinical outcomes based on referral time

	Overall (63)	Early referral (33)	Late referral (30)	p-value
OTC	6	5	1	ns
Right hepatic artery injury	8	1	7	0.022
Local initial attempt Repair	16	9	7	ns
Preop procedure (SJUH) Rx drainage ERCP PTC	19 6 11 2	8 1 6 1	11 5 5 1	ns
Injury level (Bismuth)				ns
I-II	34	20	14	
III-V	29	13 (39%)	16 (53%)	
Type of injury (Strasberg)				0.032
A-D	21	15	6	
E (complete transection)	42	18 (54%)	24 (80%)	
Morbidity				
Number of patients with complications	39	13	26	0.0001
Early complications	25	9	16	0.035

Late complications	28	10	18	0.018
Number of Readmissions	28	7	21	0.0001
Bile leak	11	3	8	ns
Cholangitis (acute)	13	7	6	ns
Cholangitis (recurrent)	22	7	15	0.017
Stricture (late)	12	5	7	ns
Reinterventions	10	2	8	0.025
Chronic pain	10	4	6	ns
HDU/ITU requirement	15	6	9	ns
Days to BDI referral*	75/4	1/1	148/17	NA
Days BDI to reconstruction*	139/16	44.14 / 3	233.9 / 88	P=0.01
Days referral to reconstruction*	60/3	42.96 / 2	77.10 / 21	ns
Referral to discharge*	112/19	48.3 / 9	176 / 59	P=0.01
Conservative treatment only**	13	11	2	0.012
Total operations per patient	2.1 (1-5)	1.8	2.5	P=0.001
Total procedures per patient	3.2 (1-7)	2.5	4	P=0.01

*mean/median days; **includes only ERCP; NA: not applicable.

Table IV. Univariate and Multivariate Analysis on Major Complications

	Major complications (Number and %)	Univariate Analysis OR (95% CI)	p	Multivariate Analysis OR (95% CI)	p
Referral					
Early	10 (15.8)				
Delayed	29 (46.0)	8.7 (2.70-28.05)	0.001	7.58(2.15-26.68)	0.002
Surgical reconstruction					
yes	35 (55.5)	4.37 (1.15-16.67)	0.031	0.23 (0.237-7.97)	0.722
no	4 (6.34)				
Strasberg classification					
A-D	7 (11.1)				
E	32 (50.8)	6.4 (2.02-20.25)	0.002	4.86(1.13-20.935)	0.033

Highlights

- Bile duct injury management in a tertiary, specialized multidisciplinary centre has favorable outcomes

- Late referral to specialist centres after bile duct injury is associated with high incidence of complications, increased need for invasive procedures and longer recovery period

- When a BDI is suspected, early referral provides the best possible outcome and is strongly encouraged