Remains of the day: Biliary complications related to single-port laparoscopic cholecystectomy

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Abstract

AIM: To assesse the rate of bile duct injuries (BDI) and overall biliary complications during single-port laparoscopic cholecystectomy (SPLC) compared to conventional laparoscopic cholecystectomy (CLC).

METHODS: SPLC has recently been proposed as an innovative surgical approach for gallbladder surgery. So far, its safety with respect to bile duct injuries has not been specifically evaluated. A systematic review of the literature published between January 1990 and November 2012 was performed. Randomized controlled trials (RCT) comparing SPLC versus CLC reporting BDI rate and overall biliary complications were included. The quality of RCT was assessed using the Jadad score. Analysis was made by performing a meta-analysis, using Review Manager 5.2. This study was based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. A retrospective study including all retrospective reports on SPLC was also performed alongside.

RESULTS: From 496 publications, 11 RCT including 898 patients were selected for meta-analysis. No studies were rated as high quality (Jadad score $\geq$ 4). Operative indications included benign gallbladder disease operated in an elective setting in all studies, excluding all emergency cases and acute cholecystitis. The median follow-up was 1 mo (range 0.03-18 mo). The incidence of BDI was 0.4% for SPLC and 0% for CLC; the difference was not statistically different ($P = 0.36$). The incidence of overall biliary complication was 1.6% for SPLC and 0.5% for CLC, the difference did not reached statistically significance ($P = 0.21$, 95%CI: 0.66-15). Sixty non-randomized trials including 3599 patients were also analysed. The incidence of BDI reported then was 0.7%.

CONCLUSION: The safety of SPLC cannot be assumed, based on the current evidence. Hence, this new technology cannot be recommended as standard technique for laparoscopic cholecystectomy.

Core tip: This study assessed the rate of Bile Duct Injuries and overall biliary complications during single port laparoscopic cholecystectomy. A systematic review of the literature was performed, including 11 randomized controlled trials (898 patients) and 60 non-randomized trials (3599 patients). No statistically significant differences were found. However, interpretation of the results was impaired by several limitations. Based on a retrospective analysis, an incidence of bile duct injuries up to 0.7% was found. The safety of single-port laparoscopic cholecystectomy cannot be assumed, based on the current evidence. Hence, this new technology cannot be recommended as standard technique for laparoscopic cholecystectomy so far.

INTRODUCTION

The recent decade has seen striking technical changes in gastrointestinal surgery. Surgeons' interest and expectations were high while waiting for the next technical evolution after laparoscopy[1]. Some of these expectations were also fuelled by industry and by patients themselves.

Traditionally, many innovations in digestive surgery were first evaluated by using cholecystectomies in humans as an *in vivo* model. The large number of patients in good condition, the non-reconstructive nature of such an intervention, and the availability of a standardized operative technique for comparison are the main characteristics predisposing gallbladder surgery to assess new technologies. Complication rates are generally low, and the only real difficulty is to avoid bile duct injuries (BDI)[2]. Indeed, BDI represent the key criteria comparing a novel technique to the current standard laparoscopic approach. The widespread implementation of conventional laparoscopic cholecystectomy (CLC) in 1990's was associated with an increased rate of bile duct injuries[3]. The lessons learnt by the clinical introduction of laparoscopy need to be re-considered since several novel techniques of minimal invasive surgery are on the point of being introduced as routine procedures in surgery without enough evidence on safety issues.

An increasingly voluminous literature on single port laparoscopic cholecystectomy (SPLC) has become available after five years of intense publications worldwide. In their meta-analysis, neither Sajid *et al*[4] nor Trastulli *et al*[5] found statistical significant differences between the two procedures in term of complications. However, BDI injuries were not analyzed specifically. On the other hand, Joseph *et al*[6] reported BDI rate as high as 0.72%, based on retrospective data.

The aim of this systematic review was to evaluate the current rate of BDI and overall biliary complication rate during single port laparoscopic cholecystectomy and to compare it with conventional laparoscopic cholecystectomy.

MATERIALS AND METHODS

Study selection

A systematic review of the literature published between January 1990 and November 2012 was performed by the first author from Medline, Embase and Web of Science databases. This search was then cross-checked by the senior author (Schäfer M). Following Medical Subject Heading (MeSH) and non-MeSH keywords were used: "cholecystectomy", "laparoscopy", "single trocar", "single port", "single incision", "single site", "single access", "trans-umbilical", "single incision laparoscopic surgery", "laparoendoscopic single site". The search was also enlarged using the "related articles" function and by manual cross-check of individual articles. A flowchart of the selection process, according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statements[7], is presented in Figure 1.

Inclusion/exclusion criteria

Initially, all clinical trials conducted on humans and reporting clearly surgical complications were included. There were no language limitations. A second step of the analysis included only randomized controlled trials. We excluded all papers not related to the subject, all series that did not report surgical complications and all series including less than 10 patients.

Outcome of interest

The primary endpoint was the rate of BDI, as described by Strasberg *et al*[2]. Secondary endpoints were the rate of overall biliary complications, defined as any complication related to the biliary system that required the readmission of patients or additional interventions, such as endoscopic retrograde cholangiopancreatography or percutaneous drainage of bilioma. The time of follow-up, the realization of intraoperative cholangiography (IOC) and the report of a true critical view were also considered.

Study quality

The quality of randomized controlled trials (RCT) was assessed using the Jadad score[8]. Studies with a score of ≥ 4 were considered high quality studies. Two reviewers (Allemann P, Schäfer M) evaluated independently all RCT included in the analysis. Results were compared thereafter and consensus were established when discrepancies were found.

Statistical analysis

Meta-analysis was conducted according to the PRISMA guideline. Investigations were performed using Review Manager 5.2 (release November 8, 2012. Cochrane Information Management System). Evaluating dichotomous variables, OR were used in the statistical analysis and favored conventional laparoscopic cholecystectomy if < 1. A statistically significant result was considered if the *P* value was < 0.05, and if the confidence interval did not include the value 1. Heterogeneity was assed using χ^2 and I^2 statistics. High I^2 and *P* value < 0.001 indicated significant heterogeneity between the studies. A power calculation was made using STATA 12.0 (Stata Corp., College Station, TX, United States), with an alpha-error of 0.05 (two sided) and a power of 80%.

RESULTS

After electronic research and manual cross match, 496 abstracts were collected. From these, 71 studies were included in the final analysis. Eleven studies were random-
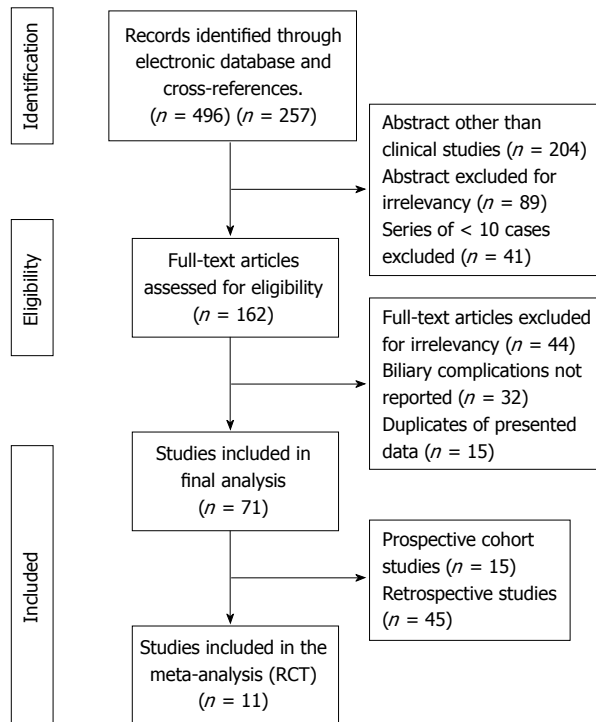
Figure 1 Flowchart diagram of the systematic review. RCT: Randomized controlled trials

Figure 2 Repartition of the studies according to Jadad score.

ized controlled trials, including a total of 839 patients (438 SPLC, 401 CLC)[9-19]. Eight series were single center[9,12,14-19], whereas the three remaining trials were multicenter studies[10,11,13]. Four studies have been performed in Asia[9,12,15,18], four in Europe[11,14,16,19], one in North America[17], one in South America[10], and one in Europe and North America[13]. Conventional laparoscopic cholecystectomy was performed with four ports in nine series[9-11,13-15,17-19] and three ports in two[12,16]. Operative indications included benign gallbladder disease operated in an elective setting in all studies, excluding all emergency cases and acute cholecystitis. Body mass index > 30 kg/m^2 was considered as a contra-indication in five studies[11-13,16,19], > 40 kg/m^2 in one study[17] and previous upper-GI surgery in eight studies[9-13,15,16,18,19]. Repartition of the studies according to Jadad score is presented in Figure 2. No studies were rated as high quality (≥ 4 points). The median follow-up was 1 mo (range 0.03-18 mo).

The incidence of BDI was 0.4% for SPLC, compared to 0% for CLC (OR = 4.5), but the difference was not statistically different ($P = 0.36$, 95%CI: 0.22-96). The heterogeneity was zero ($\chi^2 = 0.00$, $df = 1$, $P = 0.95$; $I^2 = 0\%$). Of note, only two studies including 148 patients contributed to the analysis, while the remaining nine studies were not included because no events were observed in both groups. Forrest plots are presented in Figure 3A.

The incidence of overall biliary complication was also higher for SPLC compared to CLC with 1.6% *vs* 0.5% (OR = 3.2), but again, the difference did not reached statistical significance ($P = 0.21$, 95%CI: 0.66-15). The heterogeneity was zero ($\chi^2 = 0.84$; $I^2 = 0\%$). Six studies including 482 patients contributed to the analysis.
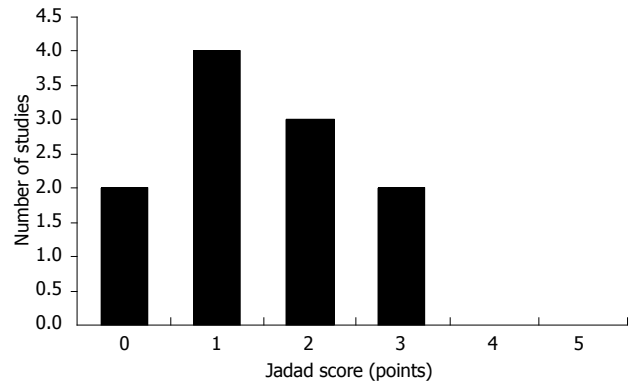
Five studies were not included because no events were observed in both groups. Forrest plots are presented in Figure 3B.

Three of 11 studies reported a perioperative assessment of the critical view of safety, for a total of 119 patients. The use of intraoperative cholangiography was also described in three studies for a total of 77 patients. The procedure was performed in 100%, 70% and 5% of SPLC patients, respectively.

For the non-randomized reports, 60 studies were included with a total of 3599 patients[20-79]. Fifteen were prospective cohort studies and 45 were purely retrospective. From this survey, 25 BDI were reported. The BDI rate was 0.7% and the overall biliary complication rate was 2%. The distribution of BDI according to the Strasberg classification[2] is presented in Figure 4; 12/25 cases of BDI were type-A injuries, and 5/25 were reported, but not specified otherwise. The overall surgical complication rate was 5%. One third (62/180) of them were related to the surgical site (seroma, hematoma, infection, hernia). In particular, 18 postoperative hernias were reported (overall hernia rate of 0.5%). The median follow-up of patients was 2 mo (range 0.03-24 mo) (Table 1).

DISCUSSION

This meta-analysis assessed the risk of BDI and other biliary complications of single port access cholecystectomy; and compared it to conventional laparoscopic cholecystectomy. The analysis of the current literature revealed an increased rate for BDI of 0.4% and other biliary complications (1.6%) compared to conventional laparoscopic cholecystectomy (0%, 0.5% respectively). However, the differences found were not statistically significant.

Cautious interpretation is mandatory since many limitations impact on these results. Only two series contributed to the analysis of the BDI rate[11,12] and this is strictly not enough to build a statistically valid analysis. Moreover, the quality of these RCT was low, as Jadad scores were not above three, as illustrated in Figure 2. For example, still many investigators use envelope-based randomization technique, and/or blinding is not systematically performed. As stated by Baum[80], overcoming the
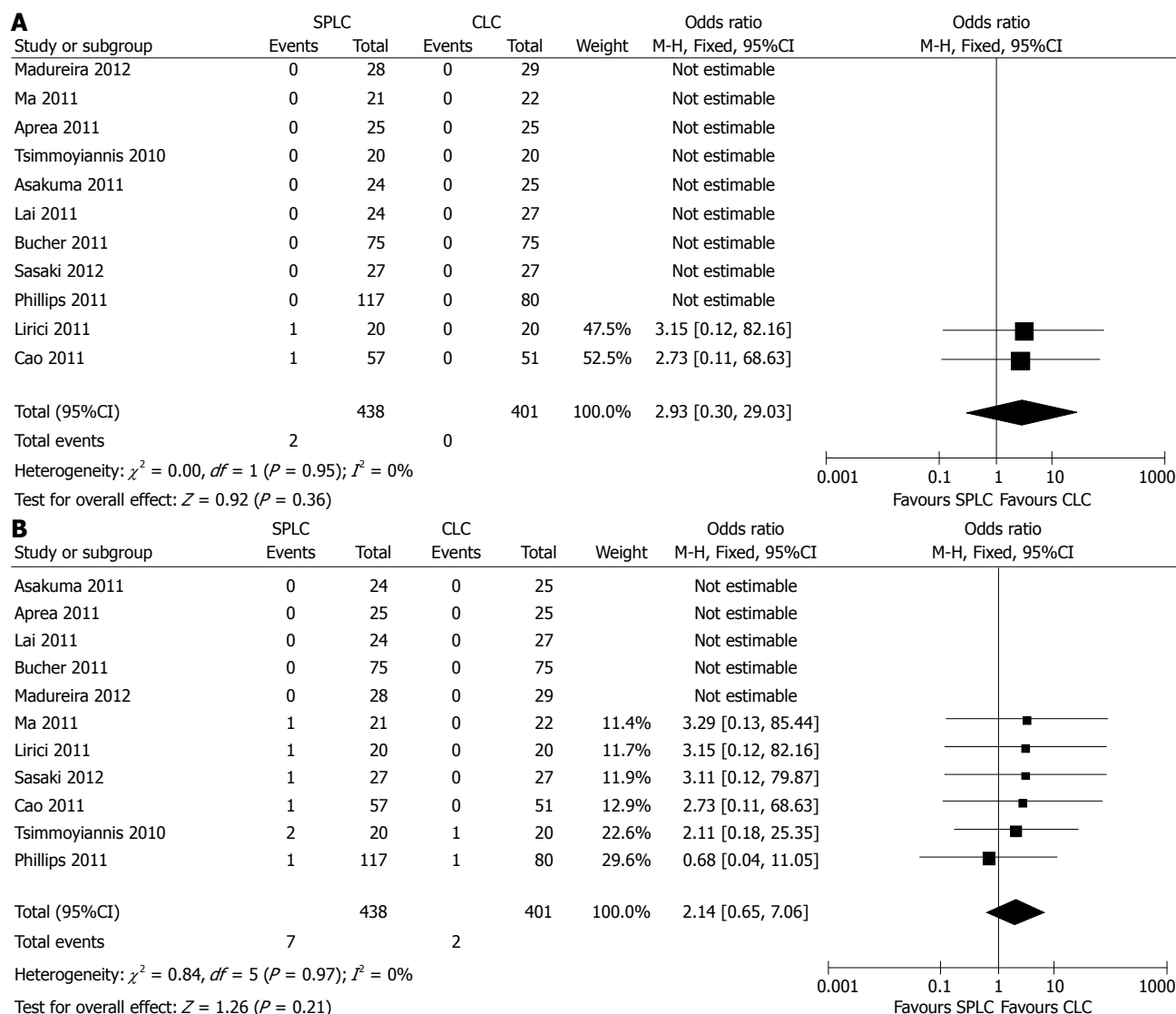
A

Study or subgroup	SPLC Events	Total	CLC Events	Total	Weight	Odds ratio M-H, Fixed, 95%CI	Odds ratio M-H, Fixed, 95%CI
Madureira 2012	0	28	0	29		Not estimable	
Ma 2011	0	21	0	22		Not estimable	
Aprea 2011	0	25	0	25		Not estimable	
Tsimmoyiannis 2010	0	20	0	20		Not estimable	
Asakuma 2011	0	24	0	25		Not estimable	
Lai 2011	0	24	0	27		Not estimable	
Bucher 2011	0	75	0	75		Not estimable	
Sasaki 2012	0	27	0	27		Not estimable	
Phillips 2011	0	117	0	80		Not estimable	
Lirici 2011	1	20	0	20	47.5%	3.15 [0.12, 82.16]	
Cao 2011	1	57	0	51	52.5%	2.73 [0.11, 68.63]	
Total (95%CI)		438		401	100.0%	2.93 [0.30, 29.03]	
Total events	2		0				

Heterogeneity: $\chi^2 = 0.00$, $df = 1$ ($P = 0.95$); $I^2 = 0\%$
Test for overall effect: $Z = 0.92$ ($P = 0.36$)

0.001 0.1 1 10 1000
Favours SPLC Favours CLC

B

Study or subgroup	SPLC Events	Total	CLC Events	Total	Weight	Odds ratio M-H, Fixed, 95%CI	Odds ratio M-H, Fixed, 95%CI
Asakuma 2011	0	24	0	25		Not estimable	
Aprea 2011	0	25	0	25		Not estimable	
Lai 2011	0	24	0	27		Not estimable	
Bucher 2011	0	75	0	75		Not estimable	
Madureira 2012	0	28	0	29		Not estimable	
Ma 2011	1	21	0	22	11.4%	3.29 [0.13, 85.44]	
Lirici 2011	1	20	0	20	11.7%	3.15 [0.12, 82.16]	
Sasaki 2012	1	27	0	27	11.9%	3.11 [0.12, 79.87]	
Cao 2011	1	57	0	51	12.9%	2.73 [0.11, 68.63]	
Tsimmoyiannis 2010	2	20	1	20	22.6%	2.11 [0.18, 25.35]	
Phillips 2011	1	117	1	80	29.6%	0.68 [0.04, 11.05]	
Total (95%CI)		438		401	100.0%	2.14 [0.65, 7.06]	
Total events	7		2				

Heterogeneity: $\chi^2 = 0.84$, $df = 5$ ($P = 0.97$); $I^2 = 0\%$
Test for overall effect: $Z = 1.26$ ($P = 0.21$)

0.001 0.1 1 10 1000
Favours SPLC Favours CLC

Figure 3 Forest plot. A: Outcome: BDI; B: Outcome: Overall biliary complication. SPLC: Single-port laparoscopic cholecystectomy; BDI: Bile duct injuries; CLC: Conventional laparoscopic cholecystectomy.
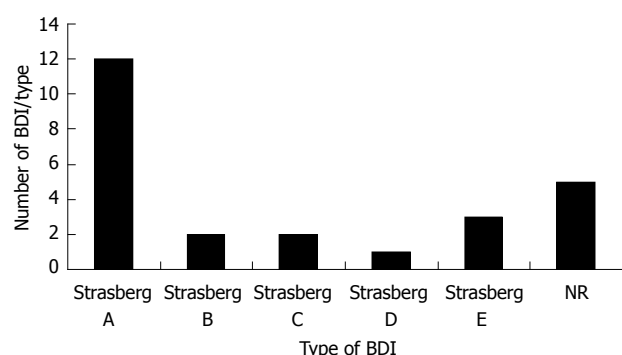
Figure 4 Repartition of the type of bile duct injuries. BDI: Bile duct injuries.

ring bile duct complications may be underreported. Only three studies reported a follow-up of ≥ 6 mo[10,13,18]. One third of the reports described follow-up of ≤ 2 wk. Of greatest relevance, even after pooled analysis, is that few patients could be satisfactorily included in the meta-analysis. This is probably the main limitation of our current review. Indeed, since the incidence of BDI is < 1%, large patient numbers are needed to detect the true incidences and its differences. A power calculation based on previous retrospective data[6] revealed a total of 14048 patients would be needed in order to detect a statistically significant difference in terms of BDI rate. This means that all RCT included in this review were clearly underpowered and sample sizes were too small to assess events with a low incidence. As seen with historical comparisons between laparoscopic and open cholecystectomy, RCT will possibly never answer this thorny issue and a larger international prospective database will be more appropriate in this setting.

ongoing allegation that research in surgery is not more than a "comic opera" requires that the surgical community has to make efforts to realize high quality trials. An important shortcoming of published series is the lack of a long-term follow-up, meaning that late occur-

Table 1 Data of the non-randomized trials

Serie	Year	n	BDI	Overall compl
Cuesta *et al*[20]	2008	10	0	0
Palanivelu *et al*[21]	2008	10	1	2
Rao *et al*[22]	2008	20	0	0
Hodgett *et al*[23]	2009	29	0	3
Hong *et al*[24]	2009	15	0	0
Kravetz *et al*[25]	2009	20	0	0
Kuon Lee *et al*[26]	2009	37	1	2
Langwieler *et al*[27]	2009	14	0	0
Merchant *et al*[28]	2009	21	0	0
Philipp *et al*[29]	2009	29	0	6
Podolsky *et al*[30]	2009	15	0	3
Tacchino *et al*[31]	2009	12	0	2
Vidal *et al*[32]	2009	19	0	0
Zhu *et al*[33]	2009	10	0	0
Garijo Alvarez *et al*[34]	2010	30	1	3
Brody *et al*[35]	2010	56	0	2
Carr *et al*[36]	2010	60	0	4
Chow *et al*[37]	2010	41	1	1
Curcillo *et al*[38]	2010	297	1	26
Edwards *et al*[39]	2010	80	3	7
Elsey *et al*[40]	2010	238	0	5
Erbella *et al*[41]	2010	100	0	0
Fronza *et al*[42]	2010	25	0	3
Fumagalli *et al*[43]	2010	21	0	2
Hu *et al*[44]	2010	32	0	0
Ito *et al*[45]	2010	31	0	0
Rawlings *et al*[46]	2010	54	0	2
Rivas *et al*[47]	2010	100	1	1
Roberts *et al*[48]	2010	56	2	3
Romanelli *et al*[49]	2010	22	0	1
Roy *et al*[50]	2010	50	1	2
Schlager *et al*[51]	2010	20	1	1
Kim *et al*[52]	2010	56	1	2
Yu *et al*[53]	2010	33	0	0
Duron *et al*[54]	2011	43	0	0
Han *et al*[55]	2011	150	2	15
Jacob *et al*[56]	2011	36	1	2
Khambaty *et al*[57]	2011	81	0	0
Kilian *et al*[58]	2011	16	0	0
Krajinovic *et al*[59]	2011	50	0	5
Kupcsulik *et al*[60]	2011	30	0	1
Li *et al*[61]	2011	51	0	8
Mesas Burgos *et al*[62]	2011	10	0	0
Mutter *et al*[63]	2011	61	0	0
Prasad *et al*[64]	2011	100	0	0
Qiu *et al*[65]	2011	56	0	3
Raakow *et al*[66]	2011	200	2	11
Rup *et al*[67]	2011	101	0	5
Vermulapalli *et al*[68]	2011	205	3	9
Vrzgula *et al*[69]	2011	100	1	5
Wen *et al*[70]	2011	50	0	2
Wu *et al*[71]	2011	100	1	3
El-geidie *et al*[72]	2012	67	0	1
Feinberg *et al*[73]	2012	50	0	2
Kehagias *et al*[74]	2012	60	0	0
Koo *et al*[75]	2012	100	0	6
Oruc *et al*[76]	2012	25	0	1
Sasaki *et al*[77]	2012	114	1	10
Wong *et al*[78]	2012	20	0	1
Yeo *et al*[79]	2012	60	1	7
Total		3599	26	180
			0.7%	5.0%

BDI: Bile duct injuries.

Unable to assess clearly the safety issue of SPLC based

on the meta-analysis, we decided to perform a second enquiry including larger non-randomized prospective and retrospective studies[20-79] in order to increase the sample size, accepting a lower grade of evidence and a higher risk of bias. The incidence of BDI was then found to be as high as 0.7%, three-times greater than the majority of recent large reviews concerning conventional laparoscopy[81-83]. This result was slightly lower than the rate reported by Joseph *et al*[6] in their analysis, probably due to a larger sample size and more recent included series. Ominously, one third (8/25) of the BDI reported in our retrospective review were Strasberg type-B or more, indicating a possible tendency for more complex injuries (Figure 4). This aspect could be underestimated, as 20% of BDI were not described or classified by the authors.

Being aware of a potentially increased rate of BDI, different strategies have been proposed to decrease this unacceptably high risk. Only three out of eleven studies used IOC, with suboptimal technical success rate (62%, 77/124 attempts)[14,16,18]. This may be explained by the need of precision and dexterity required to perform IOC, both lacking in SPLC setting. However, the true impact of this aspect remains unclear, as the discussion on the role of IOC during cholecystectomy is a never-ending story[84,85]. Although described for many years as a critical step to limit BDI during CLC, the use of the so-called "critical view of safety" was clearly reported as *a sine qua non* condition before clipping and dividing the cystic duct in three trials only[11,14,18]. Most often, this was done by the exchange of the dissecting tools for an extra-grasper, in order to gain the right exposure.

Finally, more attention should be paid by the surgeons in critically evaluating their experience with SPLC and in defining the criteria for safety. This aspect is still clearly inadequate in the current literature, as eight studies of the retrospective pool concluded that SPLC was safe, while reporting BDI or increased overall complication rates. Moreover, the hypothesis that the avoidance of 5 mm trocars as in SPLC is of significant clinical benefit was challenged by no-one.

In conclusion, the BDI rate during SPLC seems to be comparable to standard CLC at first sight, but the overall quality of RCT remains low, failing to present any convincing evidence thus far. Larger retrospective data confirm the doubt about the safety of these procedures. Based on the current evidence, SPLC cannot currently be recommended as standard technique for laparoscopic cholecystectomy.

ACKNOWLEDGMENTS

COMMENTS

Background

Single port laparoscopic cholecystectomy (SPLC) is a new technical refinement of endoscopic surgery, which has emerged more than five years ago. The basic

concept of laparoscopy remains intact, but all the instruments are introduced in the abdominal cavity through one single site (usually the umbilicus, but other locations have also been described). The goal of this modification is to decrease the surgical trauma on the abdominal wall, by decreasing the number of necessary ports. On the other hand, due to the loss of triangulation between the instruments, this technique appears technically more difficult to perform.

Research frontiers

Early in its use, this technique was used to perform cholecystectomy. After many years of practice, literature failed to shows important clinical advantages (in terms of pain reduction, length of hospital stay and cosmetic results), when compared to conventional laparoscopic cholecystectomy.

Innovations and breakthroughs

Inadvertent events after SPLC have already largely been covered in other meta-analyses. They concluded that the complication rate was similar between this approach, when compared to conventional laparoscopy. However, these studies were not specifically focused on bile duct injuries. Because this type of complication carries a much more significant potential of decreased quality of life and even mortality, authors considered that safety of SPLC should be evaluated in the light of bile duct injuries (BDI) rate, instead of overall complication rate.

Applications

As long as no stronger evidence concerning biliary safety is provided, SPLC cannot currently be recommended as standard technique for laparoscopic cholecystectomy. It appears mandatory that future studies should focus on longer follow-up of the patients. Owing to the relatively low incidence of complications, it seems evident that only large prospective nationwide cohort studies will be adequate to meet the endpoint of biliary safety. Randomized controlled trials will invariably fail to enroll enough patients to delineate such a small difference.

Peer review

Two peer reviewers contributed to the revision of this manuscript. They recognized that this serious complication should be carefully assessed, before considering a wide acceptation of this new surgical approach. If the conclusion of this manuscript is that literature failed to close the debate, this does not imply a rejection of this new technique. On the contrary, more efforts should be made to continue evaluating SPLC in the light of biliary complications. According to their comments, details on the type of BDI were added. In particular, the distribution of these complications, according to Strasberg classification, was detailed in the results and discussed in the conclusion. Moreover, more information was given concerning the distribution of overall complications.

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