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Original Article

Implementation of enhanced recovery after surgery (ERAS) in laparoscopic left lateral hepatectomy on hepatocellular carcinoma patients: necessary or not?

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Abstract: In this study, we aim to determine the application of enhanced recovery after surgery (ERAS) in single incision and multiple ports laparoscopic hepatectomy. Ninety-five patients undergoing laparoscopic left lateral hepatectomy for hepatocellular carcinoma (HCC) were included and divided into three groups: pre-MPH group (n=35), received pre-ERAS multiple ports procedures; SPE group (n=27), received single port ERAS procedures; MPE group (n=33) received multiple ports ERAS procedures. Outcomes were compared in terms of operative related outcomes, liver functional recovery, postoperative complications, hospital stay, hospitalization expense and readmissions. There were no significant differences in the prevalence of complication (P=0.601), hospital stay (P=0.645) and total cost (P=0.297) between pre-MPH group and MPE group. No readmission was noticed within 30 days after surgery in each group. No significant differences were observed in blood loss (P=0.086), resection margin (P=1.000) and mobility rate (P=0.425) between SPE group and MPE group. The operation time was shorter in the patients received single port surgery compared to these received multiple ports surgery (P=0.032). The levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were increased on day 1 after surgery, and decreased to normal level on day 5 in the three groups. ERAS programs might be not necessary for patients underwent laparoscopic left lateral hepatectomy. The perioperative outcomes are similar between multiple ports and single port laparoscopic left lateral hepatectomy.

Keywords: Enhanced recovery after surgery, single port, laparoscopy, liver surgery

Introduction

Laparoscopic hepatectomy has been commonly used for the management of patients with hepatocellular carcinoma as it shows favorable short- and long-term outcomes [1-3]. Compared to the open hepatectomy, laparoscopic hepatectomy shows several benefits such as safety, fewer complications, lower transfusions rates and blood loss and reduced hospital stay [1, 4], as well as similar 1-year, 3-year, and 5-year overall survival (OS)] [1, 3, 5]. Nevertheless, the morbidity rates remain high in liver resection [6-8], which are independently associated with decreased long-term survival in clinical practice [9, 10]. Therefore, it is crucial to minimize the morbidity for patients underwent laparoscopic hepatectomy.

Enhanced Recovery After Surgery (ERAS) programs, associated with reduced hospital morbidity and mortality, have been utilized in many specialties including colorectal surgery, urology, thoracic surgery, vascular and orthopedic surgery. Nowadays, ERAS gains increasing interest in liver resection as it is associated with reduced morbidity rates and total hospital length of stay in open and laparoscopic liver resections [11-15]. However, the impacts of introducing an ERAS program on the patients undergoing laparoscopic hepatectomy including single incision and multiple ports laparoscopic left lateral resections are still not well defined.

In this study, we aim to investigate the efficiency of ERAS in the management of single incision

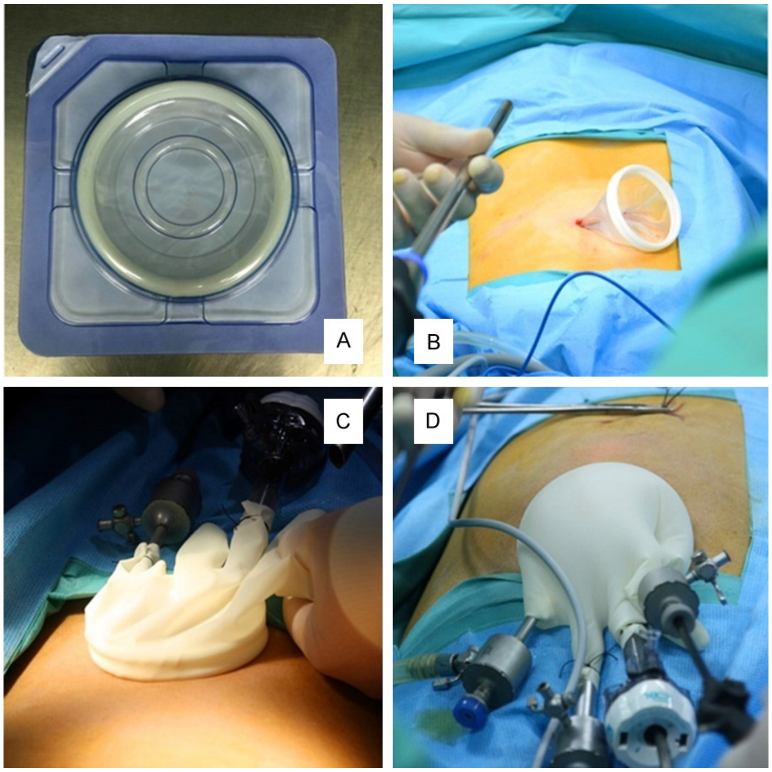

Figure 1. Surgical apparatus in single port laparoscopic left lateral hepatectomy. A and B: Showed a 4 Fr incision protector was used in single port laparoscopic left lateral hepatectomy. C and D: Showed any of the glove fingers could be a channel where we distributed surgical trocar.

and multiple ports laparoscopic hepatectomy. Besides, we investigated the effectiveness and safety of single port versus multiple ports laparoscopic surgery for hepatocellular carcinoma (HCC).

Materials and methods

Study population

Ninety-five patients with primary HCC underwent laparoscopic left lateral hepatectomy in the Department of General surgery, Qilu Hospital of Shandong University from June 2011 to May 2016 were enrolled in this study. The study protocols were in consistent with the Declaration of Helsinki. The study protocols were approved by the Ethical Committee of Qilu Hospital of Shandong University.

Study design

The patients were divided into three groups, including pre-MPH group (n=35), received pre-ERAS multiple ports procedures; SPE group (n=27), received single port ERAS procedures; MPE group (n=33) received multiple ports ERAS procedures. ERAS programs of laparoscopic liver resection were implemented in 2012.

Preoperative and postoperative measurement

Each patient received preoperative imaging including chest x-ray, abdominal ultrasonography, abdominal computed tomography. Serological tests including blood count, biochemical tests, and serum tumor markers were performed. Liver function was evaluated before surgery, and postoperative day 1, day 3 and day 5, respectively. Surgical complications were graded according to the Clavien-Dindo classification.

Surgical procedures

Conventional laparoscopic left lateral hepatectomy was performed by our same surgical team as the previous study [16].

For the single port laparoscopic left lateral hepatectomy, the procedures were performed under general anesthesia with the patients lying in a supine position. A sterile glove was used to form an invagination with a 4 Fr incision protector after a surgical incision (3 cm) was made under the umbilical area. Each of the glove finger could serve as a channel for the surgical trocar (**Figure 1**). No hepatic pedicle control was used during liver resection.

The transection line was marked on the capsule and the parenchyma transection was performed using an ultrasonic dissector (Ethicon Endo-Surgery, USA). Haemostasis was carried out using a hemo-lock and an argon knife (Force Argon II, USA). The left triangular ligament and coronary ligament were sectioned before exposure of the hepatic vein to facilitate its control. The hepatic pedicle was cut off by endovascular staplers (60 mm, Ethicon Endo-surgery, LLC, USA), after liver parenchyma exci-

Table 1. Clinical characteristics of the patients in the three groups

	Pre-MPH (n=35)	SPE (n=27)	MPE (n=33)	A*	A**	A***
Age (years)	50.34±12.75	48.44±10.24	51.94±8.75	0.621	.298	0.458
Sex				0.983	0.852	0.924
Male	16	12	15			
Female	19	15	17			
Child-Pugh class						
A	33	26	33		NA	
B	2	1	0			
ASA				0.853	0.916	0.662
I	12	11	13			
II	23	16	20			
HBsAg				0.891	0.681	1.000
(+)	31	25	29			
(-)	4	2	4			
Tumor sizes	5.02±2.01	5.50±2.26	5.24±2.19	0.732	.741	0.812

A*: Inter-group comparison among pre-MPH, SPE, MPE groups. A**: Comparison between SPE and MPE groups. A***: Comparison between pre-MPH and MPE groups.

sion (about 1 cm in depth). The specimen is entrapped in an Endocatch TM II bag through the open incision. No drainage was used in this procedure.

Endpoints

The primary endpoints included the postoperative hospital stay and complications. The secondary endpoints were readmissions and the hospitalization expense.

Perioperative management

ERAS protocol amended from the initial model to liver surgery [17] was used for the perioperative management. Low dose of opioids (Dezocine Injection, 10 mg/250 ml NS) by vein drip plus patient-controled opiate was used for the analgesia. No oral analgesia drugs were used except intolerable pain. No nasogastric intubation and drainage duct were used. One kind of acid-suppressive drug (pantoprazole, 40 mg/100 ml NS. ivdrip bid) was used.

Statistical analysis

Data analyses were performed using the SPSS 18.0 software (SPSS, Chicago, IL, USA). Continuous data with a normal distribution were statistically tested using Student's t-test. Ordinal data were analyzed using the Mann-Whitney U test. Readmission, complications were analyzed using the chi-square test or Fisher exact test. P<0.05 was considered to be statistically significant.

Results

Patient characteristics

There were no significant differences in age, sex, Child-Pugh classification, ASA physical status, HBsAg and tumor sizes between the 3 groups (**Table 1**).

Comparison of perioperative parameters

The mean operation time was 99.38±19.91 min in SPE group, 122.35±37.67 min in Pre-MPH group and 124.41±40.35 min in MPE group, respectively. Statistical analysis showed no difference among the mean operation time among the three groups. The operation time was shorter in SPE group compared with MPE group (P=0.032). There were no significant differences in blood loss among the three groups (P=0.325). No patients required RBC transfusion. No patients were transferred to open surgery, and no one required conversion to multiple ports procedures in the single port group. Verified R0 resection margins were observed in 33 (94.3%) patients in Pre-MPH group, 26 patients (96.3%) in the SPE group and 31 (93.4%) patients in the MPE group. No significant differences were noticed in the number of patients with verified R0 resection margins among the three groups (P=0.910). In the pre-MPH group, 33 underwent insertion of naso-

Table 2. Perioperative parameters in the three groups

Variable	Pre-MPH (n=35)	SPE (n=27)	MPE (n=33)	A*	A**	A***
Operative time	122.35±37.67	99.38±19.91	124.41±40.35	0.320	.032	0.920
Stapler	8	27	5	0.034	0.001	0.891
Blood loss	73.85±37.48	59.38±22.13	79.41±39.76	0.325	.086	0.812
Conversion to open	No	No	No		NA	
Resection margin				0.910	1.000	1.000
R0	33	26	31			
R1	2	1	2			
RBC transfusion	0	0	0		NA	
Nasogastric decompression tube	33	0	0		NA	
Drainage placement	30	0	0		NA	

A*: Inter-group comparison among pre-MPH, SPE, MPE groups. A**: Comparison between SPE and MPE groups. A***: Comparison between pre-MPH and MPE groups.

Table 3. Perioperative details and outcomes

Variable	Pre-MPH (n=35)	SPE (n=27)	MPE (n=33)	A*	A**	A***
Oral intake	28.6±7.8	12.8±3.6	12.5±2.8	0.001	0.872	0.001
hospital stay, d	6.76±0.98	5.68±1.36	6.15±1.39	0.702	0.480	0.645
Readmission <30 d	0	0	0		NA	
Cost (10^4/Yuan)	4.92±0.63	4.73±0.56	4.55±0.58	0.520	0.394	0.297
Pain score						
Postoperative day 1	2.1±0.6	1.9±0.5	1.9±1.0	0.902	0.893	0.732
Postoperative day 3	1.3±1.0	1.3±0.6	1.3±0.9	0.980	0.920	0.954
Postoperative day 5	1.0±0.5	0.8±0.5	0.9±0.5	0.662	0.450	0.563
ALT (Unit/L)						
Preoperative	20.35±12.74	20.18±11.92	25.35±15.44	0.654	.293	0.301
Postoperative day 1	119.44±56.28	137.56±140.18	109.94±47.71	0.704	.449	0.563
Postoperative day 5	49.85±54.43	55.81±70.87	52.65±36.63	0.924	.872	0.901
AST (Unit/L)						
Preoperative	20.11±9.77	22.18±8.06	23.71±7.67	0.612	0.583	0.450
Postoperative day 1	108.74±53.34	124.50±125.02	118.18±44.13	0.870	0.846	0.744
Postoperative day 5	37.57±35.26	27.50±7.90	41.82±32.96	0.394	0.101	0.783

A*: Inter-group comparison among pre-MPH, SPE, MPE groups. A**: Comparison between SPE and MPE groups. A***: Comparison between pre-MPH and MPE groups.

gastric tube. Five patients (14.3%) received placement of a peritoneal drain at the end of operation in pre-MPH group (**Table 2**).

Comparison of perioperative details

Statistical differences were noticed in the mean time of oral intake after surgery among the Pre-MPH, SPE and MPE groups (P=0.001). In contrast, no significant differences were noticed in the hospital stay (P=0.702) and total hospitalization cost (P=0.520) among the three groups (**Table 3**). No patient was readmitted within 30 days after surgery in each group. No statistical differences were noticed in the mean pain score in each group on day 1, day 3, and day 5 after surgery.

Serum transaminase was detected every other day after surgery. The levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased on post-operative day 1 compared to the preoperative level, and decreased to normal level on post-operative day 5 in each group (**Table 3**). The ALT and AST among the three groups showed no statistical difference in the pre-operative level, and post-operative day 1 or day 5, respectively.

Table 4. Postoperative complications according to Clavien-Dindo classification

Variable	Pre-MPH (n=35)	SPE (n=27)	MPE (n=33)	A*	A**	A***
Grade I					NA	
Wound infection	0	0	0			
				0.490	0.425	0.601
Grade II					0.341	
Nausea/vomiting	3	5	4			
Hypertension	5	2	6			
Grade IIIa					NA	
Pleural effusion	4	1	2			
Bile leakage	1	0	0			
Intraperitoneal inflammation	0	0	0			
Grade IIIb					NA	
Hemorrhage	0	0	0			
Grade IVa					NA	
Postoperative liver failure	0	0	0			

A*: Inter-group comparison among pre-MPH, SPE, MPE groups. A**: Comparison between SPE and MPE groups. A***: Comparison between pre-MPH and MPE groups.

Evaluation of postoperative complications

The complications were evaluated by the Clavien-Dindo classification, which revealed that no patients suffered from wound infection in each group. In Pre-MPH group, 13 (37.1%) showed complications of Grade II (e.g. nausea, vomiting or hypertension) and IIIa (pleural effusion, bile leakage, intraperitoneal inflammation), respectively. In the SPE group, 8 patients (29.6%) showed Grade II or III complications, while in the MPE group, 12 (36.4%) showed Grade II or III complications. No patients showed grade I or IIIb or Iva complications in each group. No statistical differences were noticed in the incidence of complications among the three groups (**Table 4**).

Discussion

Compared with open hepatectomy, the minimally invasive liver resection has many advantages such as less blood loss [1, 18-20], shorter hospital stay [1, 5, 21] and similar long-term outcomes [3, 5, 18]. Nevertheless, the morbidity rate is still high in liver resection. Recently, increasing evidence indicates patients underwent ERAS after liver resection show favorable outcomes associated with shorter hospital stay and fewer complications [11, 14, 22, 23]. This leads us to investigate the efficiency of ERAS in the management of single incision and multiple ports laparoscopic hepatectomy.

In this study, our data showed there were no significant differences in postoperative complications, hospital stay, hospitalization expense and readmissions among the ERAS groups (SPE group and MPE group) and pre-ERAS group. In a previous study, postoperative complications were reported to be independently associated with decreased long-term OS [9]. In our study, total mobility rate was 37.1% (13/35) in pre-ERAS group, 29.6% (8/27) and 36.4% (12/33) in SPE and MPE groups, respectively. In the Pre-ERAS group, 1 patient (2.86%) showed slight bile leak. In total, 12 patients suffered from nausea or vomiting on postoperative day 1 and hypertension was observed in 14 patients within 12 hours post-operation. No patients suffered from postoperative hemorrhage and liver function failure.

The total morbidity rate in our study was high, but about 26.3% patients suffered from discomforts associated with anesthesia. The incidence of hepatic complications (e.g. bile leak, hemorrhage and liver failure) was rather low (1%), which may be associated with the following aspects: Firstly, advanced laparoscopic devices such as staplers, tisseel and surgicel and argon-beam surface coagulation were used in laparoscopic hepatectomy to minimize blood loss and bile leak. Secondly, FLR could adequately compensate the metabolism in liver. On this basis, serum ALT and AST were mildly elevated 1 day post-operation, and decreased to normal level on day 5 postoperation. These data validated the safety of laparoscopic left lateral hepatectomy despise its multiple ports or single port procedures.

Implement of ERAS programs may have some advantages by theory. Earlier oral intake leads to reduction of intravenous infusion of energy, while advanced and prolonged ambulation promoted gastrointestinal peristalsis and prevented venous thrombosis of lower limb. However, in this study, our data showed no patients benefited from the ERAS programs. The mild elevation of ALT and AST and low rate of liver special complications suggested the left lateral resection is indeed safe, but whether it could explain the negligible effects of ERAS remains ambiguous.

No significant difference was noticed in the pain scores in the patients received single port liver resection compared with those received multiple ports liver resection, regardless of the implement of ERAS programs. Low dose of opioids by vein drip plus patient-controled opiate was used within 48 hrs after surgery. No oral analgesia drugs were took except those suffered intolerable pain. Unexpectedly, one patient in group single port liver resection suffered from acute abdominal pain for eating spicy food postoperative 72 hrs. Sufficient pain relief and portable drainage could contribute to earlier and prolonged ambulation. No patients showed narcotic addiction and psychiatric symptoms during the operation.

Thoracic epidural analgesia was reported to associate with fewer complications [13] compared with standard care, together with analgesia control compared with local anesthetic wound infusion catheter plus patient-controlled opiate analgesia [24]. Nevertheless, it may be a risk factor for postoperative kidney failure [25] after liver resection. Local anesthetic wound infusion catheter plus patient-controlled opiate analgesia was thought to achieve a lower incidence of overall complication compared to the epidural analgesia [26]. In our study, pain could be controlled sufficiently by low dose of opioids by vein drip plus patient-controled opiate postoperative 48 hrs. In future, further randomly controlled trials are needed to assess the efficiency and safety of analgesia in laparoscopic liver resection.

Several studies have approved the safety and feasibility of single port laparoscopic hepatectomy [27-29]. Compared with those received multiple ports laparoscopic hepatectomy, patients underwent single port laparoscopic hepatectomy showed a lower volume of intraoperative blood loss and a shorter postoperative hospitalization [28, 29]. No significant differences were observed in blood lose, hospital stay and postoperative complication in patients received single port laparoscopic hepatectomy showed compared with those received multiple ports surgery. However, patients received single port laparoscopic hepatectomy showed a shorter operation time compared with those underwent multiple ports surgery. This may be associated with the utilization of staplers that may save time during the liver parenchyma transection.

There are also several limitations in our study. It is a retrospective study involving a small sample size. A non-haplotype method of liver parenchyma transaction between multiple and single port liver resection could not reflect the operation time actually.

In conclusion, no significant differences were noticed in postoperative complications, hospital stay, hospitalization expense and readmission rates between ERAS groups and pre-ERAS group. Meanwhile, no significant differences were observed in blood loss, hospital stay and postoperative complication between multiple ports and single port laparoscopic left lateral hepatectomy. The application of staplers might save the operation time during the liver parenchyma transection. Perioperative outcomes are similar between multiple ports and single port laparoscopic left lateral hepatectomy.

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Disclosure of conflict of interest

None.

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