






Laparoscopic splenectomy and azygoportal disconnection combining with pre- and postoperative endoscopic intervention - A sandwich-style sequential therapy for portal hypertensive bleeding: A retrospective cohort study

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ABSTRACT

Background/Aims: In patients who survive the first esophageal variceal bleeding (EVB) resulting from portal hypertension, the probability of fatal esophageal variceal re-bleeding (EVR) is high. We have developed a sandwich-style sequential therapy combining laparoscopic splenectomy and azygoportal disconnection (LSD) with preoperative and postoperative endoscopic intervention (LSDE). The aim of the present study was to investigate whether LSDE is safe and effective and to evaluate whether the postoperative EVR rate for LSDE was lower than that for LSD without periodical postoperative endoscopic intervention (NLSDE).

Materials and Methods: We retrospectively investigated the outcomes of 226 patients with cirrhosis with EVB and secondary hypersplenism who all received preoperative endoscopic variceal ligation (EVL) to manage emergency EVB then underwent NLSDE (n=106) or LSDE (n=120) between February 2012 and April 2016. The perioperative and follow-up variables of the two groups were evaluated.

Results: Between the two groups, there were no differences in number of blood transfusions, intraoperative blood loss, postoperative complications, and hospital stay. LSDE showed shorter operation time (p=0.001) and lower EVR rates during the periods ranging from 1 to 12 months, 4 to 6 months, 4 to 12 months, and 7 to 12 months (all p<0.05) than NLSDE. Dynamic changes in the diameter of the esophageal varices and the rates of EVL in the LSDE group both decreased gradually and significantly over the 12-month follow-up period (all p<0.0001).

Conclusion: Laparoscopic splenectomy and azygoportal disconnection with periodical postoperative endoscopy is safe and effective for reducing the EVR rate in cirrhotic portal hypertension.

Keywords: Laparoscopy, splenectomy, azygoportal disconnection, endoscopy, cirrhosis

INTRODUCTION

Bleeding from ruptured gastroesophageal varices is the most common cause of death in patients with cirrhotic portal hypertension. At present, the main prophylactic treatments for esophageal variceal bleeding (EVB) include endoscopic variceal ligation (EVL), drug therapy, endoscopic injection sclerotherapy, surgery, and transjugular intrahepatic portosystemic shunting (TIPS) (1-4). In patients who survive the first EVB, the probability of fatal esophageal variceal re-bleeding (EVR) increases to 60% with a mortality rate of up to 33% (5). Although EVL is an effective method for the treatment of EVB, the short-term EVR rate after the first EVL was reported to be 7.8% (26/342) within the first 13 days (4,6). Of the 26 patients, 7 (26.9%) died despite positive rescue. Liang et al. also found that

β -blockers or proton-pump inhibitors are useless for the prevention of short-term EVR after EVL (4). A retrospective study of endoscopic injection sclerotherapy for portal hypertensive EVB reported that the EVR rate is increased at 36.2% (104/287), whereas the cumulative overall survival rates are 67% and 42% at 1 and 3 years, respectively (3). Furthermore, there were many complications following endoscopic injection sclerotherapy including mucosal ulceration (199/287, 69.3%), esophageal stricture (25/287, 8.7%), intramural esophageal hematoma (2/287, 0.7%), and perforation of the esophagus (8/287, 2.8%), as well as death due to perforation of the esophagus (5/287, 1.7%).

Franchis and Baveno (7) suggested that early TIPS within 72 h should be performed for patients facing high-risk

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treatment failure. However, mortality still remains high after TIPS, mostly due to worsening liver function (8).

The Hassab procedure (splenectomy and azygoportal disconnection) is a common technique in Asia for portal hypertension with EVB and secondary hypersplenism. A previous study reported the EVR and mortality rates after Hassab surgery at 8.57% (3/35) and 5.71% (2/35), respectively, during hospitalization (15.31 ± 2.410 days) and 27.27% (9/33) and 6.06% (2/33), respectively, during long-term follow-up (37.03 ± 15.551 months) (2). In China, the EVR rate after azygoportal disconnection reportedly ranges from 13.3% to 21.09% (9).

The EVR rates of these treatments were overwhelmingly unsatisfactory, mainly owing to the fatal EVR outcome. Timing of re-measurement could be important for the prevention of EVR (10). To decrease the EVR rate after EVL, we developed sequential therapy combining laparoscopic splenectomy and azygoportal disconnection (LSD) with periodical postoperative endoscopy every 3 months within the first postoperative year. To our knowledge, this is the first study of sequential therapy performed as a treatment strategy for the prevention of EVR. This retrospective study compared the postoperative EVR rates in patients with EVB and secondary hypersplenism who received LSD with periodical postoperative endoscopy with those in patients who underwent LSD without periodical postoperative endoscopy.

MATERIALS AND METHODS

Patients

Between February 2012 and April 2016, 274 patients in our department were diagnosed with EVB and secondary hypersplenism resulting from liver cirrhosis. Patients who were 18-80 years old, had been diagnosed with cirrhosis due to any etiology, had a history of EVB and hypersplenism secondary to portal hypertension with a platelet (PLT) count of $<50 \times 10^9/L$, did not suffer from portal vein system thrombosis (PVST) as demonstrated by ultrasonographic or computed tomography scan, had liver function of Child-Pugh A or B, had received EVL for EVB before LSD in order to manage emergency EVB and underwent LSD without conversion to laparotomy, had completed therapy, or died during the 12-month follow-up were included in the present study.

Patients with a hypercoagulable state without liver disease, any malignancy, antiplatelet agents or anticoagulation agents, oral contraceptives, peptic ulcer disease, uncontrolled hypertension, human immunodeficiency

virus infection, or a history of hemorrhagic stroke were excluded from the study.

Before May 2014, no patients who underwent LSD received periodical postoperative endoscopy. From May 2014 onwards, before the operation, each patient was informed that sequential therapy combining LSD with periodical postoperative endoscopy was a new treatment strategy for preventing EVR but was in the experimental stage in comparison with LSD without periodical postoperative endoscopy. The treatment strategy was performed according to the patient's choice. Ultimately, 226 patients satisfied the inclusion criteria, in which 106 underwent LSD without postoperative endoscopic intervention (NLSDE group) and 120 underwent LSD with periodical postoperative endoscopic intervention (LSDE group). Each operation was performed by the same surgical team. Written informed consent was provided by each patient. The ethics committee of the Clinical Medical College of Yangzhou University approved the present study. The work was in line with the Strengthening the Reporting of Cohort Studies in Surgery criteria (11).

A retrospective analysis was performed for the clinical data. Preoperative data included age; sex; etiology contributing to cirrhosis; Child-Pugh classification; white blood cell (WBC), hemoglobin (Hb), PLT, total bilirubin (TBIL), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine (Cr) levels; longitudinal diameter of the spleen; and main portal vein diameter. Intraoperative data comprised operation time and intraoperative blood transfused and blood loss. Postoperative data contained hospital stay, PVST at postoperative day (POD) 7, perioperative complications, and diameter of the esophageal varices of each endoscopy.

LSDE procedure

The LSD procedure has been described in our previous studies (12,13). After LSD, each patient in the LSDE group received endoscopy every 3 months in the first postoperative 12 months. During endoscopy, EVL was made if the diameter of the esophageal varices was >5 mm. If EVR recurred, emergency EVL was performed immediately. At the same time, patients who experienced EVR incidentally with EVL were registered and then removed from the subsequent research regarding the EVB rate.

NLSDE procedure

The main difference between NLSDE and LSDE was that the patients in the NLSDE group did not receive the man-

agement stratagem of periodical postoperative endoscopy, although the record of the EVR was retrospectively registered. Similarly, patients who underwent EVL for emergency EVR were registered and then removed from the subsequent research regarding the EVB rate.

Statistical analysis

Data are expressed as percentage, mean±standard deviation, or median/range. Percentages were analyzed using the chi-square test. Group means were evaluated using the Student’s t test or the Mann-Whitney U test, as appropriate. A p value <0.05 was considered as statistically

Table 1. Demographic and preoperative clinical characteristics of the NLSDE and LSDE groups

Variables	NLSDE group (n=106)	LSDE group (n=120)	p
Sex (female/male)	44/62	43/77	0.381
Age (years)	52.4±10.3	53.7±11.3	0.369
Etiology (1/2/3/4/5/6*)	69/6/7/ 2/12/10	71/9/9/ 4/14/13	0.942
Child-Pugh classification (A/B)	49/57	67/53	0.149
WBC (×109/L)	3.02±2.37	2.90±1.59	0.664
Hb (g/L)	98.3±30.0	103.4±29.4	0.202
PLT (×109/L)	39.8±8.8	41.8±8.6	0.086
INR	1.34±0.20	1.45±1.38	0.434
TBIL (µmol/L)	21.89±11.60	22.78±12.11	0.572
ALB (g/L)	37.20±6.13	37.65±7.06	0.614
ALT (U/L)	32.2±29.2	29.2±19.4	0.353
AST (U/L)	38.3±24.0	34.9±20.6	0.260
BUN (mmol/L)	5.88±2.12	5.94±2.54	0.853
Cr (µmol/L)	72.84±19.57	74.32±18.87	0.563
Longitudinal diameter of the spleen (mm)	185.8±31.0	181.4±26.6	0.255
Main portal vein diameter (mm)	14.2±2.4	14.0±2.4	0.499
Esophageal varices diameter (mm)	12.0±3.1	12.4±3.1	0.328

Data are mean±standard deviation or number of patients, as indicated

NLSDE: laparoscopic splenectomy and azygoportal disconnection without periodical postoperative endoscopy; LSDE: laparoscopic splenectomy and azygoportal disconnection with periodical postoperative endoscopy; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; INR: international normalized ratio; TBIL: total bilirubin; ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Cr: creatinine

*Hepatitis B/hepatitis C/schistosomiasis/alcohol/autoimmunity/idiopathic cirrhosis

significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 22.0 software (IBM Corp.; Armonk, NY, USA).

RESULTS

Laparoscopic splenectomy and azygoportal disconnection with periodical postoperative endoscopy was performed in 120 patients (43 females and 77 males) with EVB and hypersplenism resulting from cirrhotic portal hypertension. These patients had been admitted due to EVB. The mean age of the patients was 53.7±11.3 (20-75) years. All 120 patients suffered from hypersplenism, with a longitudinal diameter of the spleen ranging from 12.2 to 30.0 cm. The results of the patients with LSDE were compared with those of 106 patients (44 females and 62 males) who underwent NLSDE. These patients were also admitted due to EVB, with a longitudinal diameter of the spleen ranging from 11.9 to 28.0 cm. The mean age of the patients was 52.4±10.3 (26-76) years.

Table 1 shows the baseline clinical data of the NLSDE and LSDE groups. There were no significant differences with regard to age; sex; etiology of cirrhosis; Child-Pugh classification; WBC, Hb, PLT, international normalized ratio, TBIL, ALB, ALT, AST, BUN, and Cr levels; and the diameter of the spleen, main portal vein, and esophageal varices between the two groups.

Table 2 shows the intraoperative and postoperative data of the NLSDE and LSDE groups. The operation time was significantly shorter in the LSDE group than in the NLSDE group (p<0.05) (Table 2). Intraoperative blood transfused and blood loss and postoperative hospital stay were similar in the two groups (p>0.05 for all) (Table 2).

The overall rate of postoperative complication was similar between the two groups during hospitalization (p>0.05) (Table 2). None of the patients in either group suffered from incisional complications, gastric fistula, or perioperative death. There were no significant differences in the rates of emergency operations for bleeding, pneumonia, pancreatic fistula, abdominal infection, EVR, hepatic encephalopathy (HE), and PVST at POD 7 between the two groups during hospitalization.

There was no significant between-group difference in the rates of EVR during the first postoperative 3 months (p>0.05) (Table 3). However, the rates of EVR in the LSDE group were all significantly lower than those in the NLSDE group during the periods ranging from 1 to 12 months, 4 to 6 months, 4 to 12 months, and 7 to 12 months (p<0.05

Table 2. Intraoperative and postoperative characteristics of the NLSDE and LSDE groups during hospitalization

Variables	NLSDE group (n=106)	LSDE group (n=120)	p
Operation time (min)	196.2±49.4	177.4±33.1	0.001
Estimated blood loss (mL)	144.0±161.0	115.4±159.2	0.182
No. of blood transfused (n)	3	2	0.888
Postoperative hospital stay (days)	9.7±1.5	9.6±1.4	0.734
Postoperative complications	58	60	0.615
Emergency operation for bleeding	2	1	0.914
Incisional complications	0	0	-
Pneumonia	1	1	1.000
Pancreatic fistula	3	4	1.000
Gastric fistula	0	0	-
Abdominal infection	2	1	0.914
PVST (POD 7)	48	52	0.768
EVR	1	1	1.000
HE	1	0	0.950
Death	0	0	-

Data are mean±standard deviation or number of patients, as indicated

NLSDE: laparoscopic splenectomy and azygoportal disconnection without periodical postoperative endoscopy; LSDE: laparoscopic splenectomy and azygoportal disconnection with periodical postoperative endoscopy; PVST: portal vein system thrombosis; POD: postoperative day; EVR: esophageal variceal re-bleeding; HE: hepatic encephalopathy

for all) (Table 3). Among the two groups of patients with EVR, the diameter of the esophageal varices was >5 mm in 90.9% (20/22).

There was no significant difference in the rates of postoperative mortality in the NLSDE and LSDE groups (5/106 (4.7%) vs. 2/120 (1.7%); $p>0.05$). In the NLSDE group, four patients died of EVR (one at postoperative month (POM) 1, one at POM 4, one at POM 5, and one at POM 8), and one died of HE (at POM 7). In the LSDE group, two patients died of EVR at POM 2 and POM 4, respectively.

There were also no significant differences in the rates of postoperative HE (2/106 (1.9%) vs. 1/120 (0.8%); $p>0.05$) and hepatocellular carcinoma (3/106 (2.8%) vs. 2/120

Table 3. Postoperative rates of EVR of the NLSDE and LSDE groups

	NLSDE group	LSDE group	p
Total	18/106 (17.0)	4/120 (3.3)	<0.0001
POM 1-3	3/106 (2.8)	3/120 (2.5)	0.878
POM 4-6	8/103 (7.8)	1/117 (0.9)	0.010
POM 4-12	15/103 (14.6)	1/117 (0.9)	<0.0001
POM 7-12	7/94 (7.4)	0/115 (0)	0.003

Data are number of patients (percentage)

EVR: esophageal variceal re-bleeding; NLSDE: laparoscopic splenectomy and azygoportal disconnection without periodical postoperative endoscopy; LSDE: laparoscopic splenectomy and azygoportal disconnection with periodical postoperative endoscopy; POM: postoperative month

Table 4. Changes in the esophageal varices of the LSDE group

Time	Diameter of esophageal varices (mm)	p
Admission	12.4±3.1*; 12.4±3.2†	<0.0001 (overall)‡
POM 3	7.2±3.3‡; 7.2±3.3‡	<0.0001 (admission vs. POM 3)†
POM 6	4.0±2.2‡	<0.0001 (POM 3 vs. POM 6)‡
POM 9	3.4±1.2‡	<0.0001 (POM 6 vs. POM 9)‡
POM 12	3.2±1.0‡	0.004 (POM 9 vs. POM 12)‡

Data are mean±standard deviation

LSDE: laparoscopic splenectomy and azygoportal disconnection with periodical postoperative endoscopy; POM: postoperative month

*n=120; †n=119; ‡n=118

(1.7%); $p>0.05$) between the NLSDE and LSDE groups, respectively.

The diameter of the esophageal varices of the LSDE group gradually shortened as follows (except for two fatalities): 12.3±3.1 mm (admission), 7.2±3.3 mm (POM 3), 4.0±2.2 mm (POM 6), 3.4±1.2 mm (POM 9), and 3.2±1.0 mm (POM 12). The overall comparison of these measures was significant ($p<0.0001$) (Figure 1). Before EVL and by POM 3, the esophageal variceal diameter had decreased by 5.2±2.4 mm from its admission value in the LSDE group, which was significantly lower than that in the LSD group (7.2±3.3 mm vs. 12.4±3.2 mm; $p<0.0001$, except for one fatality). Specifically, after each EVL in the LSDE group, the diameter of the esophageal varices was smaller at POM 6 than at POM 3, smaller at POM 9 than at POM

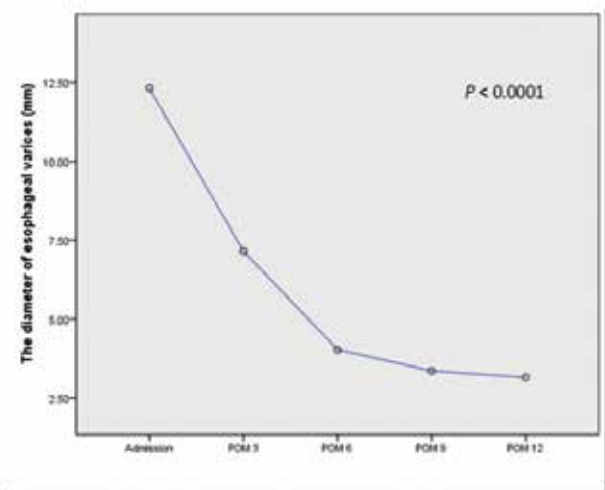


Figure 1. Dynamic changes in the diameter of oesophageal varices of the LSDE group on the day of admission and at postoperative months 3, 6, 9, and 12

LSDE: laparoscopic splenectomy and azygoportal disconnection with periodical postoperative endoscopy; POM: postoperative month

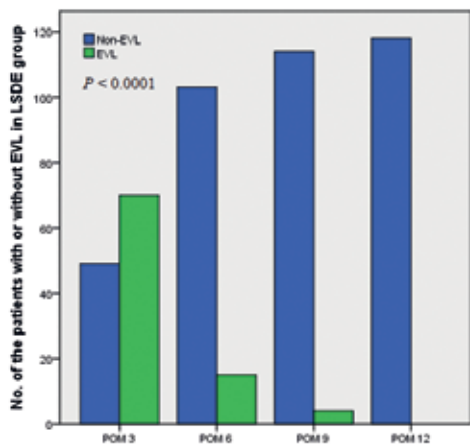


Figure 2. Dynamic changes in EVL rate of the LSDE group at postoperative months 3, 6, 9, and 12

EVL: oesophageal variceal bleeding; LSDE: laparoscopic splenectomy and azygoportal disconnection with periodical postoperative endoscopy; POM: postoperative month

6, and smaller at POM 12 than at POM 9 ($p < 0.05$ for all) (Table 4).

By POM 6, the diameter of the esophageal varices after the first postoperative EVL had decreased by 4.7 ± 1.3 mm from its POM 3 value in the LSDE group who re-

Table 5. Postoperative EVL rates of the LSDE group at different times

Time	EVR	p
POM 3	70/119 (58.8)*	<math> < 0.0001 </math> (overall)
POM 6	15/118 (12.7) [†]	<math> < 0.0001 </math> (POM 3 vs. POM 6)
POM 9	4/118 (3.4) [†]	<math> < 0.0001 </math> (POM 6 vs. POM 9)
POM 12	0/118 (0) [†]	0.130 (POM 9 vs. POM 12)

Data are number of patients (percentage)

EVL: endoscopic variceal ligation; LSDE: laparoscopic splenectomy and azygoportal disconnection with periodical postoperative endoscopy; EVR: esophageal variceal re-bleeding; POM: postoperative month

*n=119; [†]n=118

ceived EVL (n=70), which was significantly lower than that at POM 3 (4.7 ± 2.5 mm vs. 9.4 ± 2.6 mm; $p < 0.0001$). The postoperative EVL rates of the LSDE group decreased gradually. Dynamic changes in the EVL rates of the LSDE group at POM 3 (70/119 (58.8%)), POM 6 (15/118 (12.7%)), POM 9 (4/118 (3.4%)), and POM 12 (0/118 (0%)) were significant ($p < 0.0001$) (Table 5) (Figure 2). Specifically, the EVL rate was lower at POM 6 than at POM 3 and lower at POM 9 than at POM 6 ($p < 0.05$ for all) (Table 5) (Figure 2).

DISCUSSION

Treatment strategies with the lowest possible EVR rate are consistently anticipated by both patients and surgeons. Despite the fact that both EVL and azygoportal disconnection are effective methods for decreasing the EVR rate, their therapeutic effects are not overwhelmingly satisfactory, mainly owing to the serious complicating nature of EVR (2,4). Hence, the control of EVR is crucial in maintaining patient safety.

The mechanism of EVL controlling EVB arises mainly from the following two aspects: bleeding points can be managed successfully by ligation using a loop and as proven by the present study, the diameter of the esophageal varices is shortened after EVL, thus reducing the total surface area of the esophageal varices, which may contribute to decreasing the EVR by reducing friction and gastric acid corrosion on the surface of the esophageal varices.

One of the disadvantages of EVL is that it cannot block the blood flow from the portal vein directly into the esophageal varices with high-pressure perfusion. Another drawback is that the esophageal veins that are currently normal may become dilated and rupture again in the future, which is beyond the control of EVL.

The mechanisms of azygoportal disconnection and EVL for the prevention of EVR are complementary. Although azygoportal disconnection is a useful method to decrease the effect of portal hypertension on the esophageal varices by dividing the esophageal and gastric ramus communicans, its ability to shorten the diameter of the esophageal varices is limited. The reason for the outcome can be explained by a physical phenomenon likening the esophageal varices to a balloon filled with gas that remains inflated for many years. Just as the balloon can never recover its original size even after the gas is discharged, the dimensions of the esophageal varices after azygoportal disconnection may remain larger than their original size. It was demonstrated in the present study that the diameter of the esophageal varices at POM 3 after LSD (7.2 ± 3.3 mm) remained larger than normal, despite the problem being solved by EVL.

Once re-bleeding is more frequent, a second treatment in a bleed-free interval is indispensable. A previous study reported that 5 out of 19 (26%) patients who had re-bleeding in the treatment group suffer EVR before re-measurement (14). Another study showed that the possibility of EVR in patients who survive an episode of EVB is high at a rate of 60%, with a mortality of 33% (5). When is the best time to perform re-measurement? In the present study, 75% (3/4) of EVR in the LSDE group occurred within 3 months postoperatively. Hence, bringing forward the appointment to perform the first postoperative EVL ahead of schedule is worthy of consideration. Our surgical team will study this aspect further in the future.

In the present study, the sequential therapy combining LSD with preoperative and postoperative endoscopic variceal ligation intervention (LSDE group) proved to be a better method to decrease the EVR rate in comparison with NLSDE. Emergency EVB always leads to growing ascites, worse liver function, poorer coagulation function, and higher Child-Pugh classification scores, whereas EVL can temporarily solve emergency EVB, thus patients gained a chance to have sufficient time to diminish ascites and improve liver function, coagulation function, and Child-Pugh classification score, which can benefit to decrease the operative risk.

No one in the LSDE group suffered EVR from POM 6 onward, and the diameter of the esophageal varices decreased gradually through the application of periodical EVL. The diameter of the esophageal varices of all patients in the LSDE group was <5 mm up to POM 12. Moreover, the EVL rate decreased, and no patient required EVL until POM 12.

In China, the re-bleeding rate after open azygoportal disconnection is reportedly 13.3% to 21.09%, whereas in Japan, the re-bleeding rate after the modified Sugiura procedure (splenectomy, pericardial devascularization, and esophageal transection anastomosis) is reportedly $>10\%$ (9,15,16). Wang et al. (2) reported that the modified Sugiura procedure has the rates of EVR at 9.7% (3/31) and HE at 6.5% (2/31) with a mean follow-up period of 39.38 ± 14.211 months and an operative mortality of 3.2% (1/31). Moreover, in comparison with the present study, their operation time (287.1 ± 65.406 min), blood loss (431.94 ± 159.471 mL), and hospital stay (15.84 ± 2.609 days) were all higher (1). Costa Lacet et al. (17) evaluated the efficacy of the combined Hassab procedure followed by endoscopic sclerotherapy and found an EVR rate of 9.0% (2/22) which is higher than that of the present study. Furthermore, its shortage included not only big surgical trauma as a result of the Hassab procedure compared with LSD but also many complications following endoscopic sclerotherapy (3). Our results herein show an excellent 12-month control of EVR in the LSDE group with an EVR rate of 3.3%, with no EVR after POM 6 and an operative mortality of 0. A low EVR rate means low rates of mortality and re-admission and less hospitalization expense. Notably, there was no statistically significant difference in mortality rate between the groups in the present study, perhaps owing to the small sample size and short follow-up, for which the effects are more difficult to detect and/or quantify.

The low EVR rate observed in the LSDE group may be due to the effective and complementary treatment strategy combining LSD, responsible for the disconnection of the varices of the serosal layer, with EVL, dealing with the superficial esophageal varices of the mucosa. In addition, preoperative EVL is an important treatment in dealing with perforations in bleeding esophageal varices and acting as a buffer between EVB and the next operation.

Compared with the NLSDE group, except those who underwent additional postoperative EVL, the advantage of the LSDE group showed lower postoperative rates of EVR, which means decreasing the risk of liver function damage, even death. Therefore, a stable condition enables patients who are in the waiting list for transplantation to have plenty of time to wait for a donor. In addition, compared with the traditional procedure of open splenectomy and azygoportal disconnection, postoperative intraperitoneal adhesion of LSD was greatly improved, reducing the difficulty of liver transplantation due to intraperitoneal adhesion.

Laparoscopic splenectomy and azygoportal disconnection with periodical postoperative endoscopy has been

proven to be a minimally invasive surgery associated with less surgical trauma, minimal scarring, better recovery, and lower inflammatory responses than open procedures (12,18-21). Given also the minimally invasive approach of EVL, preoperative EVL and sequential therapy combining LSD with periodical postoperative endoscopy promise less surgical trauma for patients with portal hypertension.

The present study demonstrates that LSDE is technically safe and feasible. This treatment strategy not only gradually shortened the diameter of the esophageal varices but also effectively decreased the postoperative EVR rate. Randomized controlled trials with a large sample size and a long-term follow-up are required to verify these findings.

Ethics Committee Approval: The authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Written informed consent was obtained from the patients who participated in the present study.

Peer-review: Externally peer-reviewed.

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