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Selective Inflow Occlusion Technique Versus Intermittent Pringle Maneuver in Hepatectomy for Large Hepatocellular Carcinoma

A Retrospective Study

Peng Zhu, MD, Binhao Zhang, MD, Rui Wang, MD, Bin Mei, MD, Qi Cheng, MD, Lin Chen, MD, Gang Wei, MD, Da-feng Xu, MD, Jie Yu, MD, Hua Xiao, MD, Bi-xiang Zhang, MD, and Xiao-ping Chen, MD

Abstract: Selective inflow occlusion (SIO) maneuver preserved inflow of nontumorous liver and was supposed to protect liver function. This study aims to evaluate whether SIO maneuver is superior to Pringle maneuver in patients undergoing partial hepatectomy with large hepatocellular carcinomas (HCCs).

Between January 2008 and May 2012, 656 patients underwent large HCC resections and were divided into 2 groups: intermittent Pringle maneuver (IP) group (n = 336) and SIO group (n = 320). Operative parameters, postoperative laboratory tests, and morbidity and mortality were analyzed.

In comparison to the IP maneuver, the SIO maneuver significantly decreased intraoperative blood loss (473 vs 691 mL, $P = 0.001$) and transfusion rates (11.3% vs 28.6%, $P = 0.006$). The rate of major complication between the 2 groups was comparable (22.6% vs 18.8%, $P = 0.541$). Patients with moderate/severe cirrhosis, total bilirubin > 17 μmol/L, or HBV DNA>=104 copy/mL in SIO group resulted in lower major complication rates.

The SIO maneuver is a safe and effective technique for large HCC resections. In patients with moderate/severe cirrhosis, total bilirubin > 17 μmol/L, or HBV DNA>=104 copy/mL, the SIO technique is preferentially recommended.

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Abbreviations: ALT = alanine aminotransferase, AST = aspartate amino transferase, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, IP = intermittent Pringle maneuver, PT = prothrombin time, SIO = selective inflow occlusion maneuver.

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From the Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.
Correspondence: Bi-xiang Zhang, Xiao-ping Chen, Department of Surgery, Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (e-mail: bixiangzhang@163.com and chenxp@medmail.com.cn).
PZ, BZ, and RW contributed equally to this work.
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INTRODUCTION

Hepatocellular carcinoma (HCC) is a highly prevalent and lethal cancer. It is estimated that 500,000 to 1 million annual cases are reported worldwide,[1] especially in the Asia-Pacific region. Partial hepatectomy is a potentially curative therapy for HCC patients,[2–4] but liver resection may present intraoperative bleeding. Moreover, bleeding together with the subsequent blood transfusions can increase postoperative morbidity and mortality.[5,6] In addition, blood transfusions, even in small volumes, have been found to enhance tumor recurrence in patients undergoing surgical excision of the HCC.[7–9]

Hepatic vascular control is effective in minimizing intraoperative bleeding during hepatectomy, especially for large tumors or those located in proximity to major vascular structures.[3,10–12] The Pringle maneuver, a technique of transient hepatic inflow occlusion by clamping the portal triad, is the simplest and most established method for controlling afferent blood flow. However, the Pringle maneuver carries the risk of ischemia-reperfusion injury to liver, particularly in patients with chronic hepatic cirrhosis[3,12–14] Ischemia-reperfusion injury caused by temporarily interrupted blood inflow to liver is a complex, multifactorial pathophysiologic process that includes intrahepatic adenosine-5?-triphosphate (ATP) depletion, oxidative stress, and generation of inflammatory mediators.[15,16]

Selective inflow occlusion (SIO) techniques, with continuous occlusion of hepatic artery and intermittent occlusion of the portal vein supplying the tumor-containing portion of the liver, have been applied to reduce blood loss and injury to the liver function.[17] In this study, this maneuver was applied to decrease ischemia-reperfusion injury of the remnant liver, especially for patients with cirrhosis. The advantage of this maneuver is to provide continuous arterial inflow of nontumorous liver by the hepatic artery during surgery.

Until now, the clinical advantage of using either the SIO or intermittent Pringle maneuvers (IPs) remained unclear. To address this issue, a retrospective study was designed to evaluate these 2 vascular control methods during large HCC resections.

PATIENTS AND METHODS

Patients

From January 2008 to May 2012, we evaluated 656 large HCC cases in our department. This study was approved by the Ethics Committee for Clinical Pharmacology in Tongji Medical College, and all the information of patients were kept private. Large HCC was defined with a tumor diameter >= 5 cm. Based on the maneuvers of hepatic vascular occlusion, these patients were divided into 2 groups: IP group (n = 336) and SIO group

(n = 320). The diagnoses of cirrhosis and HCC were confirmed by histological studies of the surgical specimens. The following patients were excluded from this study: patients with a history of previous liver resection, patients with other concomitant major surgical procedures, such as splenectomy, bowel resection, bile duct resection, and esophageal devascularization. Data were recruited consecutively to address potential sources of bias.

Preoperative Evaluation

All patients had a chest X-ray, abdominal ultrasonography, and computer tomography portography vascular imaging. Preoperative laboratory blood tests included hemoglobin, platelet count, alanine aminotransferase (ALT), aspartate amino transferase (AST), serum albumin, serum total bilirubin, alkaline phosphatase, γ-glutamyl transferase, cholesterol, indocyanine green retention at 15 minutes after intravenous injection, creatinine, prothrombin time (PT), fibrinogen, hepatitis B surface antigen, hepatitis C antibody, and serum alpha-fetoprotein. Child–Pugh score was used to assess hepatic function for each patient. No patient received preoperative transcatheter hepatic arterial chemoembolization treatment.

Surgical Procedure

All surgical procedures were accomplished by 4 experienced liver surgeons from the same department, ensuring procedures performed in a standardized manner. Intraoperative ultrasonography was routinely used in all patients to assess the number and size of the tumors, and their relation to nearby vascular structures. The hepatic parenchyma was transected using an ultrasonic scalpel. Liver resections based on segmental anatomy were performed in all patients.

In SIO group, the portal vein, proper hepatic artery, right and left hepatic arteries, and bile ducts were dissected. The hepatic artery in the tumor bearing lobe was continuously blocked with a bulldog clamp. The portal vein was encircled with a rubber tourniquet in advance. During the parenchymal transection, all vessels and bile ducts were ligated on the preserved side. Small hepatic venous bleeding was ligated or coagulated. Intermittent portal vein occlusion was tightened when more bleeding from portal vein system was encountered during transection. Finally major hepatic vein was doubly ligated and divided.

In IP group, hepatic vascular control was performed through encircling the hepatoduodenal ligament with an umbilical tape and then applying a tourniquet until the pulse in the hepatic artery disappears distally. The porta hepatis was intermittently clamped with cycles of 15 minutes of inflow occlusion followed by 5 minutes of reperfusion.

Anesthetic management was accomplished by general anesthesia, and blood loss was estimated by taking into account suction volume minus rinsing fluids. Indications for red blood

TABLE 1. Clinical Characteristics of HCC Patients

Variable	Intermittent Pringle Maneuver (n = 336)	Selective Inflow Occlusion (n = 320)	P^*
Age, year	46.4 (28–62)	45.2 (27–61)	0.381
Sex (male%)	285 (85%)	284 (89%)	0.487
Hepatitis B carrier, %	292 (87%)	268 (84%)	0.660
HBV, $\log_{10}$copy/mL	5.51 (3.13–6.82)	4.76 (2.75–7.33)	0.001
Liver function status			0.865†
Child–Pugh A	240	224	
Child–Pugh B	96	96	
Cirrhosis, %	256 (76%)	256 (80%)	0.577†
Preoperative laboratory tests			
Hemoglobin, g/L	139.0 (111–170)	137.8 (97–167)	0.646
Platelet count, 109/L	199.8 (11–353)	178.4 (36–343)	0.075
ALT, U/L	39.4 (19–87)	43.1 (11–128)	0.360
AST, U/L	44.4 (18–111)	45.3 (12–96)	0.810
Albumin, g/L	36.2 (27.7–42.1)	37.1 (29.7–45.9)	0.185
Bilirubin, μmol/L	14.4 (8.4–57.6)	15.4 (5.3–27.9)	0.509
Prealbumin, mg/L	67.2 (18–271)	63.6 (51–298)	0.285
ALP, U/L	105.5 (62–211)	101.8 (40–205)	0.541
GGT, U/L	150.3 (25–825)	111.8 (14–576)	0.114
Cholesterol, mmol/L	4.01 (2.44–11.56)	3.98 (2.72–5.48)	0.882
ICG-15, %	13.9 (5.4–26.0)	14.3 (4.9–24.0)	0.681
Creatinine, μmol/L	63.5 (47–81)	61.4 (44–86)	0.206
PT, s	11.8 (9.4–15.0)	11.8 (10.2–13.7)	0.894
PTA, %	102.8 (12–158)	95.7 (67–127)	0.054
Fibrinogen, g/L	3.72 (2.34–4.81)	3.65 (2.57–4.81)	0.435
AFP, $\log_{10}$ng/mL	2.2 (0–5)	2.3 (0–5)	0.797

Values are mean (range). AFP = alpha-fetoprotein, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma glutamyl transferase, HCC = hepatocellular carcinoma, HBV = hepatitis B virus, ICG = indocyanine green retention, PT = prothrombin time, PTA = prothrombin activity.

* Student's *t*-test.

† Except χ^2 test.

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TABLE 2. Pathological Factors of Hepatocellular Carcinoma (HCC) Patients

Variable	Intermittent Pringle Maneuver (n = 336)	Selective Inflow Occlusion (n = 320)	P^*
Tumor size, cm	8.7 (5–15)	8.7 (5–14)	0.986
Multiple tumors, %	48 (14.3%)	36 (11.3%)	0.643†
Differentiation			0.761†
High, %	24 (7.1%)	16 (5.0%)	
Medium, %	240 (71.4%)	224 (70.0%)	
Low, %	72 (21.4%)	80 (25.0%)	
AJCC/UICC staging system			0.097†
I	180 (53.6%)	208 (65.0%)	
II	92 (27.4%)	44 (13.8%)	
IIIa	64 (19.0%)	68 (21.3%)	
Type of hepatectomy			0.377†
Segment I + II + III	8	0	
Segment I + II + III + IV	4	0	
Segment II + III	32	24	
Segment II + III + IV	44	40	
Segment IV + V + VIII	40	44	
Segment V + VI + VII + VIII	96	140	
Segment V + VIII	44	28	
Segment VI + VII	68	44	

AJCC/UICC staging system indicates AJCC/UICC tumor node metastasis staging system for HCC (7th edition; 2009). Values are mean (range or percentage).

* Student's *t*-test.

† except χ^2 test.

cell transfusion included blood loss exceeding 800 mL or a hemoglobin level below 5.6 mmol/L during operation or within 48 hours after surgery.

Postoperative Management

All patients received the same postoperative care. Liver function was monitored by ALT, AST, albumin, prealbumin, bilirubin, cholesterol, prothrombin time, and fibrinogen on postoperative days 1, 3, 5, and 7. Liver cirrhosis was evaluated according to the size of cirrhotic nodules in resected specimen, as we described previously.[3] The tumors were diagnosed histopathologically. Postoperative complications and mortality within 30 days postoperatively were assessed based on the Clavien–Dindo classification.[18]

Statistical Analysis

Continuous, normally distributed variables are expressed as mean (±SD) or median (range), as appropriate. Student's *t*-test was performed for continuous data, and χ^2 test was used for categorical data. All statistical tests were 2-sided. *P* value less than 0.05 was considered statistical significant. All statistical analysis was performed with SPSS 13.0 statistical software (SPSS, Chicago, IL).

RESULTS

Baseline of Patient Characteristics

In total, 336 patients were included in IP group and 320 patients in SIO group. There was no significant difference between the 2 groups in rates of age, sex ratio, cirrhosis ratio, types of hepatectomy, and preoperative laboratory test, except hepatitis B virus (HBV) DNA level (Table 1). Hepatitis B patients were distributed homogeneously between groups. ALT, AST, and alpha-fetoprotein were higher than normal value in both groups (Table 1).

Clinicopathological Characteristics and Type of Hepatectomy

There were no significant differences between the 2 groups regarding tumor size, patients with multiple tumors, grade of tumor differentiation, and American Joint Committee on Cancer/International Union Against Cancer staging (Table 2). More than half of the patients belonged to the medium differentiation and AJCC/UICC stage I.[19] None of the patients exhibited distant metastasis. There was no significant difference in type of hepatectomy between 2 groups (Table 2).

Influence of Type of Clamping on Postoperative Laboratory Test Results

Peak values of ALT and AST occurred on the 1st day after surgery (Table 3). In most patients, AST and ALT levels returned to normal within 7 days (Figure 1). Total ALT, AST, and total bilirubin levels in IP group were significantly higher than those in SIO group, while cholesterol and fibrinogen levels in IP group were lower (Table 3). The dynamic change of transaminase, albumin, bilirubin, cholesterol, and prealbumin level on postoperative days 1, 3, 5, and 7 are shown in Figure 1. For SIO group, the cholesterol level showed an earlier increase to normal value, and the albumin level returned to baseline level on postoperative day 7. There was a significant difference in the change of prealbumin on postoperative day 5 and day 7 between 2 groups.

Influence of Type of Clamping on Operative Parameter

The intraoperative data including operative time, ischemic duration, intraoperative blood loss, and blood transfusion are

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TABLE 3. Postoperative Laboratory Test Results and Outcome Data

Variable	Intermittent Pringle Maneuver (n = 336)	Selective Inflow Occlusion (n = 320)	P^*
Nadir hemoglobin, g/dL	115.6 (21.2)	114.9 (20.4)	0.824
Nadir platelet count, $\times 10^3/\mu L$	116.9 (51.3)	120.2 (54.6)	0.695
ALT, U/L			
Peak	1101 (649)	419 (262)	**<0.001**
AUC, per day	539 (309)	205 (115)	**<0.001**
AST, U/L			
Peak	1141 (671)	374 (204)	**<0.001**
AUC, per day	410 (262)	144 (83)	**<0.001**
Albumin, g/L			
Nadir	28.2 (3.4)	29.5 (5.9)	0.097
AUC, (per day)	31.1 (3.2)	32.2 (4.4)	0.064
Total bilirubin, μmol/L			
Peak	26.0 (23.7)	17.8 (6.5)	**0.002**
AUC, per day	22.6 (16.6)	16.5 (6.6)	**0.003**
Cholesterol, mmol/L			
Nadir	2.1 (0.4)	2.6 (0.8)	**<0.001**
AUC, (per day)	2.5 (0.7)	3.0 (0.8)	**<0.001**
Prealbumin, mg/L			
Nadir	56.4 (28.6)	71.2 (45.0)	**0.013**
AUC, per day	90.1 (38.0)	97.5 (47.6)	0.270
PT, s			
Peak	14.2 (1.8)	13.7 (1.8)	0.099
AUC, per day	13.4 (1.7)	13.3 (1.5)	0.842
PTA, %			
Nadir	76.7 (15.0)	75.5 (12.6)	0.562
AUC, per day	82.8 (17.2)	80.6 (13.5)	0.364
Fibrinogen, g/L			
Nadir	3.1 (1.1)	3.3 (1.1)	0.179
AUC per day	3.4 (0.9)	3.7 (1.0)	**0.035**

Values are mean (SEM). Nadir or peak values were minimum or maximum values measured within the first 7 days after surgery. AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, AUC = area under the curve for the first 7days after surgery, PT = prothrombin time, PTA = prothrombin activity.

* Student's *t*-test.

shown in Table 4. Several patients suffered from different complications (61.9% vs 57.5%, Table 4). No patients died after the operation in any group. No patients were found to have early postoperative bleeding requiring reexploration in any of 2 groups. More than half of the patients had abdominal/subphrenic collection or pleural effusion, and only few patients suffered complications of bile leak, wound infection, or chest infection. There was no significant difference in hospital stay between 2 groups.

Risk Factors Related to Major Complications

Multivariate analysis confirmed that albumin, total bilirubin, HBV DNA, cirrhosis were related to postoperative complications morbidity (Table 5). The logistic regression analysis showed that 4 parameters were independent predictive factors for the development of complications (Table 6). The subgroup analysis showed that patients with moderate or severe cirrhosis, total bilirubin $> 17\,\mu mol/L$, or HBV DNA $>= 10^4$ copy/mL in SIO group resulted in less major complication, when compared with the IP group (Table 7). However, the type of hepatic vascular occlusion had no influence on morbidity in albumin (<35 g/L), albumin (>=35 g/L), and total bilirubin (<=17 μmol/L) subgroups.

DISCUSSION

Excessive blood loss during hepatectomy requiring perioperative blood transfusion has a negative impact on morbidity and mortality,[6,20,21] particularly in patients with cirrhosis. Using modern technology, hepatic parenchymal transection can be carried out with little blood loss. A Japanese survey revealed that only a minority (7%) of surgeons never use inflow occlusion, whereas 25% apply a Pringle maneuver on a routine basis even in cirrhotic patients.[22] Although inflow occlusion is not necessarily accepted as routine practice, many surgeons still prefer to use hepatic vascular inflow occlusion with, or without outflow occlusion during parenchymal transection,[3,12,23,24] especially in those cirrhotic patients with irregular branches and collateral circulations of vessels.

The Pringle maneuver is sufficient in most situations to control bleeding from the hepatic artery or portal vein during hepatectomy. However, it is hard to avoid ischemic injury in the remnant liver after Pringle maneuver and may result in postoperative liver dysfunction.[3,12,15,16] The degree of ischemic injury to the hepatocytes may be accentuated in the presence of underlying liver disease.[25] Therefore, several strategies have been used to minimize ischemic injury during liver surgery. Makuuchi et al[26] first interrupted long ischemic intervals during

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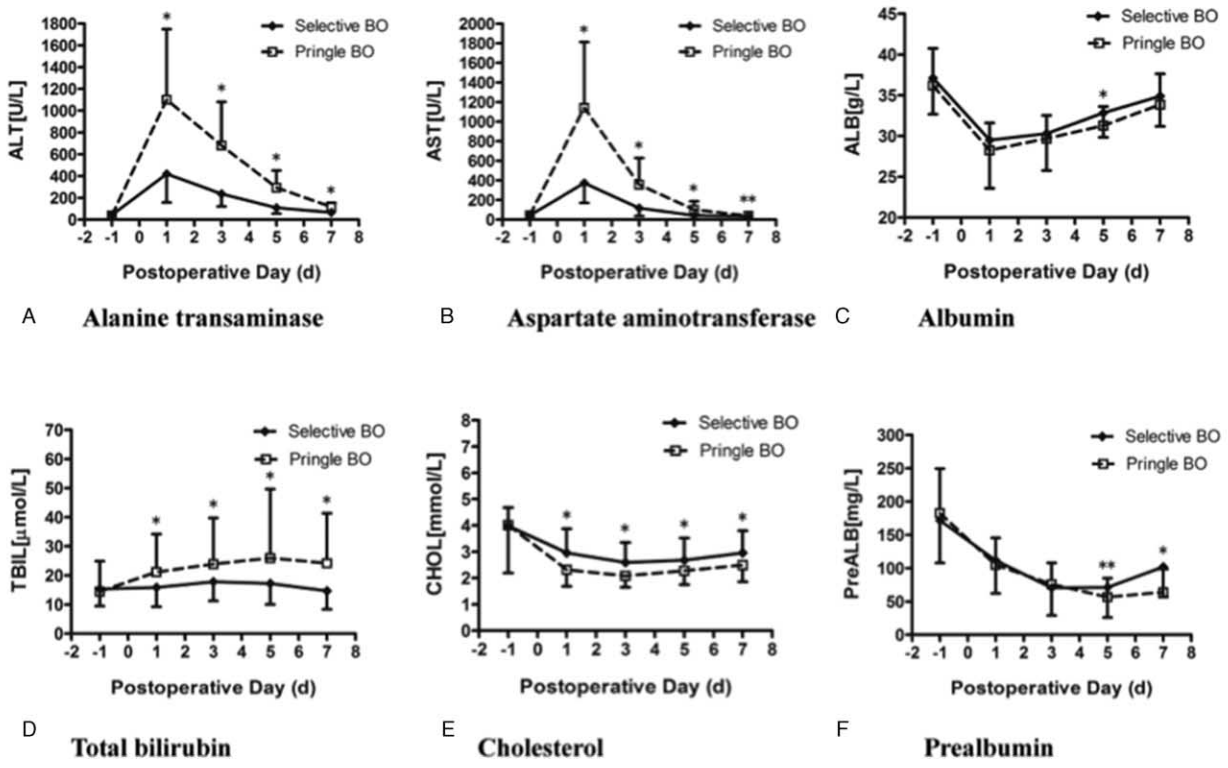

FIGURE 1. Comparison of (A) alanine transaminase, (B) aspartate aminotransaminase, (C) albumin, (D) total bilirubin, (E) cholesterol, and (F) prealbumin in patients in new selective inflow occlusion (selective BO) and intermittent Pringle maneuver (Pringle BO) groups. Serial measurements in A–F are presented as mean (SEM). $^{*}P < 0.01$, $^{**}P < 0.05$ versus Pringle maneuver (Student's *t*-test).

liver resection with short periods of reperfusion in 1980s. Belghiti et als'[27] RCT provided evidence that intermittent clamping of portal triad was superior to protect liver function when compared with continuous clamping. Thereafter, ischemic preconditioning was considered as an alternative to intermittent clamping and was proved to protect liver from injury.[28] In addition, more than 80% of HCC patients suffer from HBV infection in China,[3,4,10,11] which also contributes to a different degree of cirrhosis. For these patients, choosing an inflow occlusive maneuver during liver resection still warrants further study.

Since 1963, continuous selective inflow occlusion of the hepatic artery supplying the tumor-containing segments of liver plus intermittent occlusion of the portal vein has been applied to reduce blood loss and injury to the liver function.[17] The main concern over the SIO maneuver is whether there is an increase in ischemic complications, especially when the occlusion is required for a long time. In the Cochrane review by Gurusamy et al,[29] there was no evidence to support SIO over portal triad clamping. However, all trials in this review were of high risk of bias. Our data showed that intraoperative blood loss (473 vs 691 mL) and perioperative blood transfusion (11.3% vs 28.6%) in SIO group were significantly less than those in the IP group, although the ischemic duration was longer (25.2 vs 17.9 minutes). The difference might be caused, in part, by different parenchymal transection speed. Further the work of hemostasis may not be performed until the transection is finished. This was confirmed by results of blood loss and blood transfusion rates. Based on our data, liver function was less intensely influenced and recovered more quickly in SIO group when compared with IP group. This could be explained by less impairment of hepatic metabolism and synthesis function as a consequence of continuous arterial infusion of remnant liver in the SIO group.

In 2006, Clavien[28] reported that the rate of overall and major (grade 3–5) postoperative complications with IP maneuver was 37.8% and 27%. In 2010, Fu et al[23] reported that overall postoperative complication and operative mortality rates for liver resection under total hepatic vascular exclusion were 53% and 2%. In this study, only 60 patients (18.8%) with SIO maneuver suffered from major postoperative complications, and no patient died in the SIO group. Four patients with hepatic insufficiency recovered and were discharged. All of these findings confirm that the SIO maneuver is safe and well-tolerated compared with the IP maneuver and total hepatic vascular exclusion.

Multiple European-based studies[6,30] have confirmed that hepatitis C virus related cirrhosis, intraoperative bleeding volume, high central venous pressure, low lactate clearance, and hepatic venous pressure gradient > 10 mmHg are the main predictor for hepatic decompensation after hepatectomy, especially in patients with liver cirrhosis. Further multivariate analyses demonstrated that initial central venous pressure higher than 9 mmHg, initial HVPG higher than 10 mmHg, and intraoperative bleeding volume were independent predictors related to postoperative morbidity.[6,30,31] However, there is controversy about the clinical importance of these factors in Asian countries. For instance, most HCC patients in oriental countries are HBV-infected.[3,32] As Makuuchi[33] and Fan[34,35] revealed, selection of candidates for liver resection relies on Child–Pugh classification and indocyanine green retention at

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TABLE 4. Comparison of Operative Parameters and Outcomes of Hepatocellular Carcinoma (HCC) Patients

Variables	Intermittent Pringle Maneuver (n = 336)	Selective Inflow Occlusion (n = 320)	P^*
Operative time, min	282 (190–410)	277 (170–450)	0.618
Ischemic duration, min	17.9 (11–32)	25.2 (13–50)	**<0.001**
Intraoperative blood loss, mL	691 (50–2030)	473 (100–1250)	**0.001**
Transfusion requirements			
Patients transfused, %	96 (28.6%)	36 (11.3%)	**0.006**†
Packets red cell, mL	750 (400–1200)	711 (600–800)	0.671
Overall complications	208 (61.9%)	184 (57.5%)	0.634†
Grade 1			
Wound infection	12	8	
Grade 2			
Pleural effusions (not requiring aspiration)	100	108	
Peritoneal effusions	84	100	
Pulmonary problems	12	12	
Total minor complications (Grade 1 + 2)	132 (39.3%)	124 (38.8%)	0.944†
Grade 3			
Pleural effusions (requiring aspiration)	64	52	
Bilioma/bile leak	12	8	
Intra-abdominal bleeding	0	0	
Grade 4			
Grade 4a (single organ dysfunction)	4	4	
Grade 4b (multiorgan failure)	0	0	
Grade 5			
Death	0	0	
Total major complications (Grade 3 + 4 + 5)	76 (22.6%)	60 (18.8%)	0.541†
Hospital stay (day)	25 (18–44)	25 (16–57)	1.000

Values are mean (range or percentage).
* Student's *t*-test.
† except χ^2 test.

TABLE 5. Risk Factors for Major Complications According to Multivariate Analysis

Variables	Unstandardized Coefficients		
	B	Std. Error	*P*
Age, year	0.010	0.058	0.865
Preoperative laboratory tests			
Platelet count, 10^9/L	0.048	0.034	0.151
ALT, U/L	−0.110	0.081	0.180
AST, U/L	0.064	0.087	0.459
Albumin, g/L	−0.134	0.056	**0.018**
Total bilirubin, μmol/L	0.449	0.136	**0.001**
Cholesterol, μmol/L	−0.008	0.048	0.866
Prothrombin activity, %	−0.133	0.093	0.155
HBV-DNA, $\log_{10}$copy/mL	−0.140	0.035	**0.000**
TNM	−0.033	0.058	0.565
Blood loss, mL	0.000	0.000	0.134
Blood occlusion maneuvers	0.185	0.119	0.123
Cirrhosis	0.523	0.064	**0.000**

ALT = alanine aminotransferase, AST = aspartate aminotransferase, HBV-DNA = hepatitis B virus deoxyribonucleic acid.

15 minutes retention test, while hepatic venous pressure gradient is not routinely measured and used to decide whether it is appropriate for operation or not. Therefore, we could not use these factors to evaluate the risk of postoperative complication, which is also one of the main limitations of this retrospective study. Based on our results, cirrhosis (moderate and severe), total bilirubin (>17 μmol/L), albumin (<35 g/L), and HBV DNA ($>10^4$ copy/mL) are independent predictive factors for the development of postoperative complications. Albumin not only plays an important role in maintaining the fluid balance between the intravascular and extravascular compartments,[36] but can also

TABLE 6. Risk Estimate of Factors Related With Major Complications

	OR (95% CI)	*P*
Cirrhosis (moderate or severe)	67.167(21.485–209.973)	<0.001
Albumin (>35 g/L)	0.137(0.060–0.315)	<0.001
Total bilirubin (>17 μmol/L)	6.575(2.889–14.964)	<0.001
HBV-DNA (<10^4copy/mL)	0.255(0.114–0.570)	0.001

CI = confidence interval, HBV-DNA = hepatitis B virus deoxyribonucleic acid, OR = odds ratio.

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TABLE 7. Comparison of Postoperative Complications According to Different Risk Factors

	Intermittent Pringle Maneuver			Selective Inflow Occlusion			
	Minor	Major	n	Minor	Major	n	P^*
Cirrhosis							
No or slight	128(50%)	0(0%)	256	108(39.7%)	32(11.8%)	272	**0.016**
Moderate or severe	4(5%)	76(95%)	80	16(33.3%)	28(58.3%)	48	**0.034**
Albumin							
<35 g/L	32(33.3%)	48(50%)	96	28(25%)	44(39.3%)	112	0.303
>=35 g/L	100(41.7%)	28(11.7%)	240	96(46.2%)	16(7.7%)	208	0.749
Total bilirubin							
<=17 μmol/L	132(43.4%)	44(14.5%)	304	72(37.5%)	16(8.3%)	192	0.353
>17 μmol/L	0(0%)	32(100%)	32	52(40.6%)	44(34.4%)	128	**0.004**
HBV-DNA							
<104 copy/mL	0(0%)	16(33.3%)	48	48(42.9%)	48(42.9%)	112	**0.001**
>=104 copy/mL	132(45.8%)	60(20.8%)	288	76(36.5%)	12(5.77%)	208	**0.009**

HBV-DNA = hepatitis B virus deoxyribonucleic acid.
* χ^2 test.

modulate hyperinflammatory responses after surgery through scavenging free radicals and reactive inflammatory mediators in the intravascular compartment.[37] Many studies[38,39] have confirmed that albumin administration may improve outcomes with respect to morbidity and mortality in liver disease or hypoalbuminemia patients. So, we routinely recommend the administration of 20% albumin to correct serum levels up to 30 g/L during perioperative period.

As we know, each hepatic vascular occlusion technique has its place in liver surgery. Tumor location, underlying liver disease, the experience of the surgical, and anesthetic team should be taken into account to select the appropriate method for achieving hepatic vascular control in a given patient. Based on the findings of this study, we recommend that the SIO maneuver has superiority over the IP maneuver in terms of parenchymal tolerance to ischemia for patients with moderate or severe cirrhosis, total bilirubin > 17 μmol/L, or HBV DNA >=10^4 copy/mL, if needed. Recent study[32] confirmed that partial hepatectomy for HBV-related HCC induced HBV reactivation in a proportion of patients. We recommend antiviral therapy for those patients with HBV DNA more than 500 copy/mL and close monitoring with HBV DNA in the perioperative period for all patients with HBV-related HCC.

As far as the limitation is concerned, it is a retrospective study with limited number of patients in a single center. Risk of bias still existed, although it was performed in a consecutively manner. A randomized clinical trial with larger number of patients would provide stronger evidence to get a conclusion.

One of the potential drawbacks of applying selective inflow occlusion is to perform a porta hepatic dissection, although it is not difficult for experienced surgeons. When the tumor has infiltrated porta hepatis or major vessels in the hepato-duodenal ligament, it is contraindicated to apply this maneuver. The other limitation is that all conclusions from this retrospective study should be further confirmed by several prospective randomized studies with higher grade evidence.

In view of our results, we can conclude that the SIO maneuver is safe and effective. SIO has less impairment of hepatic function compared with IP. Cirrhosis (moderate or severe), total bilirubin (>17 μmol/L), albumin (<35 g/L), and HBV DNA (>10^4 copy/mL) are independent predictive factors for morbidity. For patients with moderate or severe cirrhosis, total bilirubin > 17 μmol/L, or HBV DNA >=10^4 copy/mL, SIO maneuver is preferentially recommended. We think that these conclusions may help hepatobiliary surgeons decide which maneuver to choose during hepatectomy, if occlusion is necessary.

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