

A Comparison between Low Central Venous Pressure Technique and Conventional Technique to Minimize Blood Loss during Liver Resection: a Retrospective Study

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Abstract

Background: The Low central venous pressure (LCVP) technique has been accepted as a method to minimize blood loss during liver resection. The LCVP technique intends to control the CVP levels at less than 5 mmHg. However, this technique may cause hemodynamic instability and renal complications.

Objective: This retrospective study aimed to demonstrate the benefit of the LCVP technique in terms of blood loss, vasopressors requirement, an incidence of acute kidney injury compared to the conventional technique in liver resection surgery.

Methods: After approval of IRB, the data of patients who underwent liver resection were divided into two groups; the LCVP and conventional groups. Demographic data, intraoperative vasopressors requirements, estimated blood loss (EBL), packed red blood cell (PRBC) transfusion and serum creatinine were reviewed retrospectively.

Results: One hundred thirteen patients underwent

liver resection; 57 patients received the LCVP technique while conventional technique applied to 56 patients. EBL in conventional technique group was 700 (500-1400) mL whereas in LCVP technique group was 400 (200-575) mL ($P=0.001$). Eleven (19.3%) patients in LCVP group required PRBC transfusion whereas 21 (37.5%) patients in conventional group ($P=0.032$). There was no significant difference in vasopressor requirement between groups. Lastly, the incidence of acute kidney injury (AKI) in the conventional group and the LCVP group were 3 (5.4%) and 3 (5.3%) respectively ($P=0.982$).

Conclusion: This study demonstrated the benefit of the LCVP technique in reducing blood loss and PRBC transfusion. There was no increase in vasopressor requirements or incidence of AKI in the LCVP technique compared to the conventional technique in liver resection.

Keywords: low central venous pressure, perioperative blood loss, perioperative blood transfusion

Liver resection has been a treatment of choices for hepatobiliary carcinoma, cancer with liver metastasis and non-cancer liver lesion. This operation has potentially caused significant blood loss leading to multiple blood transfusions. Consequently, perioperative blood transfusion is associated with many worst outcomes such as transfusion-related infection, increased length of hospital stay, and cancer recurrence rate.¹ There have been new strategies in either surgical or anesthetic-related management which aim to minimize blood loss or transfusion during liver resection, for example, vascular occlusion techniques, state of art surgical equipment, blood conservative methods, and low central venous pressure technique (LCVP).² Currently, the implementation of LCVP techniques has become a role of anesthetic teams to reduce blood loss in surgical fields.

LCVP technique has been world widely accepted in many institutes as a method to reduce blood loss during liver resection. Our hospital is a low to medium volume hepatobiliary surgery center performing around one hundred fifty hepatectomies a year. This technique has been applied in our center for few years but there have been inconsistent techniques and defining term of LCVP among our anesthesiologists. Moreover, maintaining of LCVP during liver resection may commonly cause unstable hemodynamics, air embolism, inadequate tissue perfusion and renal complications.^{3,4} Mostly, the prior studies aimed the CVP levels at 5 mmHg or less during liver resection which the incidence of hemodynamic instability or requirement of vasopressor treatment for hypotension was increased.^{5,6} At beginning of

the LCVP era, our anesthesiologists were afraid of those consequences, therefore we managed LCVP technique with caution and not too strict on low levels of central venous pressure which did not cause trouble on hemodynamic management. To develop protocol-guided LCVP technique management, this retrospective study aimed to demonstrate the benefit of not too strict LCVP technique in early experience of our anesthesiologists in terms of blood loss reduction, blood transfusion and renal complications compared to the conventional technique in low to medium volume hepatobiliary surgery center.

Methods

In this retrospective study, after approval of the Institutional Review Board at Mahidol University (ID 02-61-41), medical records of patients who underwent liver resection from January 2016-December 2017 in Ramathibodi Hospital were reviewed. Our study excluded patients who did not have central venous pressure monitoring, underwent laparoscopic hepatic resection, liver donor, and patients with serious surgical complications related to the inferior vena cava injury. We divided the patients into the LCVP technique group and conventional technique group. The LCVP group includes all the patients whom CVP level were kept at 8 mmHg or lower before starting transection of liver parenchyma. Whereas, patients with CVP above 8 mmHg and had no additional attempt to maintain lower CVP level were categorized in the conventional group.

Anesthetic protocol

Our standard monitor for liver resection included invasive blood pressure, EKG, pulse oximeter, temperature and central venous pressure monitor were applied in every patient. Central venous pressure transducer was zeroed at the mid-axillary line. Either general anesthesia alone or combined with thoracic epidural anesthesia was conducted. The CVP values of patients in the LCVP group were maintained at low levels during the transection phase. After liver specimen was removed, the patients in the LCVP group were given more intravenous fluid to restore intravascular volume. Mean arterial blood pressures of all patients were kept 60-65 mmHg or more. In case of hypotension, intravenous ephedrine or norepinephrine was given. Packed red blood cell (PRBC) was transfused to maintain the patients' hemoglobin between 7 to 10 g/dL. During operation, a coagulation test was selectively checked in patients with a large amount of blood loss. However, all patients were routinely checked a coagulation test in postoperative period. If the coagulation test were shown abnormal results defined by one and a half of upper normal limits, fresh frozen plasma (FFP) was transfused. A patients' estimated blood loss was summarized by anesthesiologists or nurse anesthetics after checking suction canisters and swabs.

Evaluation parameters

From medical record of each patient the following data were collected: patient demographic including age, gender, weight, height, body mass index (BMI), ASA physical status, previous abdominal surgery, comorbidity, diagnosis, and baseline laboratory values.

Intraoperative data from anesthetic records were reviewed including operation time, extent of resection, anesthetic technique, vasopressors used, estimated blood loss, amount of intravenous fluid volume and urine output. The CVP measurement in each group was collected at the lowest CVP within ten minutes before performing liver resection. Number of patients who received blood component transfusion were collected until 24 hours postoperative period. Serum creatinine level were followed until 48 hours postoperative, patients with serum creatinine rising of 0.3 mg/dL or more were defined as having postoperative acute renal injury (AKI) according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines definition.

Statistical analysis

The sample size was calculated by the mean of blood loss in LCVP group and conventional in a previous study⁷ with a type I error of 0.05 and power of 0.8. The result indicated that 28 patients were required in each group.

Continuous variables were summarized by mean with standard deviation or median with interquartile range. The Student's t test or Mann-Whitney U test was applied to assess the differences between two groups. Categorical variables were compared between the two groups using Chi-Squared test and presented as number with percentage. Binary multiple logistic regression was performed to identify independent risk factors of blood transfusion. The *P* value of less than 0.05 was a statistically significant difference. Statistical analysis was performed with SPSS version 20.0 (IBM Co., Armonk, NY., USA).

Results

During the study period, a total of 172 patients underwent open hepatectomy. We excluded 24 and 35 patients who were liver donor and who had no CVP monitoring, respectively. The remaining 113 patients were reviewed; 57 patients were categorized into the LCVP technique while the conventional technique was applied to 56 patients. Overall, forty-four patients (39%) were mainly diagnosed with primary hepatocellular carcinoma. The second most common indication was liver metastasis lesion in 29 patients (26%). In addition, nineteen patients (17%) had a cirrhotic liver preoperatively. The patients' demographic data, comorbidities and preoperative laboratory data were shown in Table 1. There was no significant difference between two groups.

Intraoperative data were shown in Table 2. There were no significantly difference in operating time, anesthetic technique, and extent of resection which the majority of cases were right lobe hepatectomy (40.4%). The lowest CVP level in LCVP group were 5 (4-6) mmHg, compared to 10 (9-11) mmHg in conventional group ($P<0.001$). Intravenous fluid infusion and urine output were significantly lower in LCVP group. Vasopressor requirement (defined as patients who received ephedrine or norepinephrine, intraoperatively) were not shown statistically differences.

The median of intraoperative blood loss in the conventional group was 700 (500-1,400) mL, while in the LCVP group was 400 (200-575) mL which was significantly lower ($P=0.001$). The number of patients who received blood

component up until 24 hours postoperative period were significantly lower in the LCVP group. Looking into the details, patients in the conventional group required significantly more packed red blood cell (PRBC) transfusions than the LCVP group ($P=0.032$). The number of patients who received transfusion of fresh frozen plasma (FFP) were lower in the LCVP group but the difference did not reach a statistically significant point (Table 3). The incidence of acute kidney injury (AKI) defining by KDIGO guideline, our study found that AKI in the conventional group was 5.4% (3/56) and in the LCVP group was 5.3% (3/57), and did not show a significant difference between two groups ($P=0.982$).

Finally, all factors which associated with receiving PRBC were analyzed by univariate and multivariate analysis. (Table 4), preoperative hematocrit lower than 34%, prolongation of INR over than 1.1 and CVP level (which defined as the lowest CVP within ten minutes before performing liver resection) higher than 6 mmHg were independent risk factors associated with the need for PRBC transfusion.

Discussion

Hepatic blood flows into the liver through inflow system including the portal vein and hepatic artery. Prior to liver resection, the surgeons apply the portal triad clamping or Pringle maneuver to occlude the hepatic artery and portal vein in order to control bleeding from inflow system. However, the congestion of the hepatic vein may contribute to an increase in blood loss from surgical field. The LCVP

Table 1 Patient demographics, comorbidities and preoperative laboratory data

	LCVP group (n=57)	Conventional group (n=56)	P-value
Age (yr), mean±SD	58.88±11.23	59.50±11.49	0.771
Male , n (%)	37 (64.5)	39(65.6)	0.592
Weight (kg), mean±SD	63.57±13.37	65.78±13.09	0.376
Height (cm), mean±SD	160.63±8.63	163.85±9.31	0.059
Body mass index (kg/m ²), mean±SD	24.52±4.35	24.33±3.37	0.803
ASA physical status , n (%)			0.973
I	3 (5.3)	2 (3.6)	
II	25 (43.9)	26 (46.4)	
III	28 (49.1)	27 (48.2)	
IV	1 (1.8)	1 (1.8)	
Diagnosis , n (%)			0.952
Hepatocellular carcinoma	23 (40.4)	21 (37.5)	
Cholangiocarcinoma	12 (21.1)	11 (19.6)	
Metastasis cancer	14 (24.6)	15 (26.8)	
Gallbladder cancer	2 (3.5)	2 (3.6)	
Hemangioma	1 (1.8)	2 (3.6)	
Others	5 (8.8)	5 (8.9)	
Previous abdominal surgery , n (%)	28 (49.1)	32 (57.1)	0.393
Comorbidity , n (%)			
Cirrhosis	8 (14.0)	11 (19.6)	0.425
HBV infection	10 (17.5)	9 (16.1)	0.834
HCV infection	4 (7.0)	5 (8.9)	0.708
Diabetic mellitus	14 (24.6)	13 (23.2)	0.867
Hypertension	20 (35.1)	20 (35.7)	0.944
Chronic kidney disease	6 (10.5)	1 (1.8)	0.054
Coronary artery disease	1 (1.8)	3 (5.4)	0.300
Preoperative laboratory , mean±SD			
Hemoglobin (g/dL)	12.54±1.89	13.06±1.73	0.127
Hematocrit (%)	38.27±5.32	40.28±4.35	0.090
Platelet	232,210±71,437	286,392±61,202	0.269
INR	1.08±0.12	1.04±0.08	0.056
Serum creatinine (mg/dL)	0.89±0.39	0.87±0.23	0.978
BUN (mg/dL)	15.47±7.22	14.54±4.76	0.417
AST (U/L)	45.70±31.45	47.34±44.96	0.823
ALT (U/L)	43.30±31.45	42.14±36.31	0.875

Continuous variables are presented in mean±SD. Categorical variables are presented in number (%).

ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; LCVP, low central venous pressure.

Table 2 Intraoperative data

	LCVP group (n=57)	Conventional group (n=56)	P-value
Operative time (min), mean±SD	380.01±134.38	393.75±118.67	0.566
Extent of resection , n (%)			0.952
Right lobectomy	23 (40.4)	21 (37.5)	
Left lobectomy	12 (21.1)	11 (19.6)	
Left lateral lobectomy	14 (24.6)	15 (26.8)	
≥3 segmentectomy	0	1 (1.8)	
<3 segmentectomy	1 (1.8)	2 (3.6)	
Wedge resection	5 (8.8)	4 (7.1)	
Hepatectomy with hilar resection	2 (3.5)	2 (3.6)	
Anesthetic techniques , n (%)			0.159
GA	23 (40.4)	30 (53.6)	
Combine GA with EB	34 (59.6)	26 (46.4)	
Lowest CVP (mmHg), median (interquartile range)	5 (4-6)	10 (9-11)	<0.001*
Vasopressor requirement, n (%)	38 (66.7)	28 (50.0)	0.072
Intravenous fluid, mean±SD			
Crystalloid (mL)	2,747.54±1,332.99	3,455.45±1,387.98	0.007*
Colloid (mL)	39.47±131.86	188.75±367.74	0.005*
Urine output (mL), mean±SD	438.25±281.876	556.52±290.695	0.030*

Continuous variables are presented in mean±SD. Categorical variables are presented in number (%).

Lowest CVP is presented as median (interquartile range).

GA, general anesthesia; EB, epidural block; CVP, central venous pressure

* P ≤ 0.05 statistically significant.

Table 3 Comparison of intraoperative estimated blood loss and 24 hours blood transfusion between two groups

	LCVP group (n=57)	Conventional group (n=56)	P-value
Intraoperative blood loss (mL), median (interquartile range)	400 (200-575)	700 (500-1,400)	0.001*
Number of patients received PRBC within 24 hours, n (%)	11 (19.3)	21 (37.5)	0.032*
Number of patients received FFP within 24 hours, n (%)	11 (19.3)	20 (35.7)	0.051

Estimated blood loss are presented in median (interquartile range). Categorical variables are presented in number (%).

FFP, fresh frozen plasma; PRBC, packed red blood cell

* P ≤ 0.05 statistically significant.

Table 4 Univariate analysis and multivariate analyses of pre- and intraoperative factors and associations with the need of PRBC transfusion

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Hematocrit <34%	5.68 (1.85-17.38)	0.002*	6.61 (1.82-24.31)	0.005*
CVP >6 mmHg	2.75 (1.15-6.54)	0.021*	5.12 (1.71-14.81)	0.003*
INR >1.1	3.58 (1.48-8.67)	0.005*	3.94 (1.45-10.63)	0.011*
Age	0.90 (0.96-1.01)	0.970		
Male	1.90 (0.83-4.58)	0.125		
Operation time	1.02 (0.99-1.01)	0.134		
Cirrhosis	1.32 (0.91-2.42)	0.091		

PRBC, packed red blood cell; INR, international normalized ratio; CVP, central venous pressure; OR, odds ratio; 95%CI, 95% confidence interval

* $P \leq 0.05$ statistically significant

technique has been applied to decrease blood loss from outflow system, it has been proven the effectiveness of minimizing blood loss in liver surgery from many studies.^{2,7} Theoretically, the pressure within liver sinusoids is directly related to pressure effect of hepatic veins which were closely connected to inferior vena cava and central vein pressure. Sand and coworkers studied by insertion of microcatheters into the hepatic vein, they found that there was a direct correlation between hepatic vein pressure and central venous pressures.³ As a result, the lower pressure in the central venous caused lesser bleeding into the surgical field.^{4,6} This study supported the LCVP technique by maintaining LCVP levels decrease the amount of blood loss in liver resection.

Several studies reported risk factors of blood loss in liver surgery which found that the extension of resection, operative time and

preexisting cirrhosis were unmodifiable perioperative factors that determined the degree of blood loss.⁸⁻¹⁰ In our study, those factors were distributed equally into two groups. The previous meta-analysis showed a significant reduction of blood loss in the LCVP technique when compared to conventional technique but the mean difference in those studies which were higher than in our study.¹¹ The explanation might be that the LCVP group in our study had higher CVP levels than in the previous meta-analysis. Most of the prior LCVP studies tried to keep levels of CVP less than 5 mmHg. At our institution, the anesthesiologists were concerned about the hemodynamic instability, intraoperative venous air embolism, inadequate tissue perfusion and renal complications. Therefore, the CVP were maintained at not too low level.

There was a study showed that the peak CVP levels were associated with greater rates of

blood loss.¹² Hence, the effect of maintaining LCVP on blood loss remained to exist even the CVP levels were not less than 5 mmHg. One of the considerations in reading the CVP level is the zero setting of the pressure transducer. We tried to lay the transducer at the mid-axillary line but when the transducer was changed its location from moving the surgical table to facilitate the surgical approach depending on liver anatomy. Moreover, some studies used a reverse Trendelenburg position to lower the CVP. These would cause abrupt alteration of CVP levels which would not reflex the actual pressures inside inferior vena cava pressure or hepatic vein pressure.

Apart from the reduction of operative blood loss, another drawback of LCVP techniques is hemodynamic instability resulting from fluid restriction, nitroglycerin infusion, or diuretics which are applied to keep low CVP. Inevitably, increased hypotensive episodes which need some fluid or vasopressor resuscitation.^{6,13} In this study, we could not show the difference of the numbers of patient using vasopressors between two groups, it could be that our study did not keep the CVP levels as low as that of prior studies which mostly aimed the levels less than 5 mmHg. However, more data such as doses, numbers, or type of drugs were required to emphasize the benefit of not too low CVP level on decreasing vasopressor requirement. As our study mentioned that our team just implemented LCVP strategies into our clinical practice and has not had the protocol of LCVP management yet. Results from this study might be helpful as a guidance to develop the suitable

CVP level in LCVP technique to avoid undesirable consequences of strictly maintaining LCVP less than 5 mmHg.

Our study showed that PRBC transfusion requirement was about 37.5% in the conventional group, whereas it was only 19.3% in the LCVP group. This reduction became close to the other studies that ranged from 35-50%.^{7,14} The difference in blood transfusion rates in each study depended on preoperative patient condition, criteria for transfusion trigger and individual anesthesiologists' judgment. The requirements of FFP transfusion in both groups were almost significant difference. We hypothesized that the extension of surgery, amount of liver remaining after resection and degree of liver injury would affect the coagulation system individually.

Previous studies tried to find out predictors of blood transfusion in the liver resection, some studies had shown the factor associated with blood transfusion such as preoperative low hemoglobin, cirrhosis, large tumor, major hepatectomy, redo operation, and high CVP.¹⁵⁻¹⁷ The data from our study suggested that the low preoperative hematocrit was the strongest factor associated with the need for PRBC transfusion following by CVP higher than 6 mg/dL and INR higher than 1.1 respectively which correlated with the previous studies.

Perioperative acute kidney injury leads to severe renal dysfunction that is one of the potential devastating postoperative complications which was concerned in the LCVP technique of liver resection. Moreover, the postoperative acute kidney injury after liver resection

was associated with increased postoperative mortality.¹⁸ In the present study, the incidences of acute kidney injury were no significant difference between both two groups but the incidence of acute kidney injury in the LCVP group was quite difference from prior studies.^{3,19} The reason maybe because in some previous studies used the RIFLE or AKIN classification whereas our study used KDIGO classification for acute kidney injury diagnostic criteria. The advantage of applying KDIGO classification for diagnostic criteria of acute renal injury was shown in patients who underwent liver transplantation or major operations which showed that KDIGO classification had higher sensitivity and specificity than RIFLE classification.²⁰

This study had some limitations. There were several uncontrolled variables associated with the patient's outcomes, for example, amount of intravenous fluid, trigger hemoglobin level depending upon individual anesthesiologist's decision. As the LCVP technique had been used in our hospital only for few years, we did not standardize each our anesthesiologists' management. Lastly, our study did not include surgery techniques or experience of surgeons which may be different between the surgeons.

Conclusion

This study demonstrated the benefit of the not too strictly low central venous pressure technique for reducing blood loss and transfusion and without increased vasopressors usage or postoperative acute kidney injury. Low preoperative hematocrit, INR of 1.1 and

central venous pressure of 6 mmHg or more are independent risk factors of packed red cell transfusion in liver resection surgery.

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