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Original Article

Effect of controlled low central venous pressure technique on postoperative hepatic insufficiency in patients undergoing a major hepatic resection

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Abstract: Objective: To investigate the effect of controlled low central venous pressure (CLCVP) technique on postoperative hepatic insufficiency in patients undergoing major hepatic resection. Methods: In this single-center, propensity score matching, retrospective study, 331 patients who underwent laparoscopic major hepatectomy consecutively from October 1, 2014 to October 30, 2020 were enrolled and divided into a CLCVP group [0≤ central venous pressure (CVP) ≤5 cmH_2O] and normal CVP (NCVP) group (5< CVP ≤10 cmH_2O). The propensity score matching was used to adjust the differences in the data and was matched 1:1 to evaluate the impact of CLCVP on the incidence of liver insufficiency. Results: After propensity score matching, 84 patients were included in each group, with a good balance of preoperative baseline and intraoperative data between the two groups. The incidence of postoperative hepatic insufficiency was 21.23% in the CLCVP group, which did not differ from that in the NCVP group (21.54%) (P>0.05). Conclusion: In patients undergoing laparoscopic major hepatectomy, CLCVP technique did not increase the incidence of postoperative hepatic insufficiency.

Keywords: Central venous pressure, major hepatectomy, postoperative hepatic insufficiency

Introduction

Surgery is the most effective treatment for primary hepatocellular carcinoma. Open surgery is traditionally used for partial hepatectomy. In recent years, more clinicians have adopted laparoscopic techniques for the treatment of primary hepatocellular carcinoma, which can not only reduce surgical trauma and provide surgeons with a clear and open operative field, but also facilitate rapid postoperative recovery, shorten length of the hospital stay and improve the patient prognosis [1, 2]. However, intraoperative bleeding remains one of the common complications of liver surgery. Even with minimally invasive lumpectomy, intraoperative bleeding can be also induced by abundant hepatic blood flow, fragile liver tissue, and the complex intrahepatic vascular relationship. Therefore, prevention and control of bleeding volume are the key to successful surgery and to avoid conversion of laparoscopic surgery to open surgery. In addition, a massive volume of bleeding and intraoperative blood transfusion can increase the risk of complications and mortality of patients, affecting their long-term prognosis [3-5]. Therefore, intraoperatively anesthesiologists often performed controlled low central venous pressure (CLCVP) to assist the surgeon in reducing liver bleeding by limiting fluid intake, diuresis, and administration of vasoactive drugs to control central venous pressure (CVP) below the normal range (<5 cmH_2O) [6], which may lead to hypotension and organ hypoperfusion [7]. This hinders the perioperative recovery of liver function. As a result, whether the perioperative CLCVP affects the recovery of postoperative liver function still lacks sufficient clinical evidence.

The aim of this study was to assess the relationship between CLCVP and postoperative hepatic insufficiency in patients undergoing laparoscopic major hepatectomy.

Materials and methods

Data collection

This was a propensity score-matched, retrospective study, and data were collected retrospectively through an electronic medical record system. The study protocol was reviewed and approved by the Ethics Committee of The First People's Hospital of Chongqing Liang Jiang New Area (Chongqing, China). Since this study is a retrospective study, written informed consent was not required by the ethics committee, and patient privacy was kept strictly confidential.

Recruitment of patients

Patients who underwent laparoscopic major hepatectomy in our hospital from October 1, 2014 to October 30, 2020 were screened through the electronic medical record system. Inclusion criteria: hepatocellular carcinoma was confirmed by pathologic sections, with American Society of Anesthesiologists (ASA) grade I-III and age ≥18 years. Exclusion criteria: patients with severe preoperative cardiopulmonary and renal insufficiency, abnormal coagulation, conversion to open surgery, blood loss ≥1000 mL, and incomplete clinical data were excluded.

Study grouping

Patients were divided into a CLCVP group (observation group, 1≤ CVP ≤5 cmH_2O) and the NCVP group (control group, 5< CVP ≤10 cm H_2O).

Anesthetic management

All patients were routinely monitored for electrocardiogram (ECG), pulse oximetry, and noninvasive blood pressure before induction of anesthesia, and continuous arterial blood pressure monitoring and blood gas analysis were performed by radial artery puncture under local anesthesia. Other intraoperative monitoring included end-expiratory carbon dioxide, nasopharyngeal temperature, and urine output.

Since they were managed anesthetically by the same team, all patients received similar general anesthesia by tracheal intubation with induction by etomidate, sufentanil, and cis-atracurium besylate. The intraoperative Bispectral Index (BIS) values were maintained at 40-60 with sevoflurane, while sufentanil and cis-atracurium besylate were given intermittently, and intraoperative inhaled oxygen concentration was 80% in all cases. Puncturing of the internal jugular vein was performed at the end of induction for CVP monitoring. CLCVP was performed as determined by the surgeons, including 15° head over feet, control of pneumoperitoneum pressure, and rehydration volume prior to the parenchymal dissection of the liver. Vasoactive drugs were administered to maintain CVP at 1-4 cmH_2O and mean arterial pressure (MAP) >60 mmHg. After hemostasis, blood volume was rapidly supplemented at 1:1 with crystalloid colloid to maintain CVP >5 cmH_2O. Blood transfusion was performed when hemoglobin <7.0 g/dL. For patients comorbid with cardiovascular disease, blood transfusion was performed when hemoglobin <10.0 g/dL.

At the end of the surgery, whether patients were transferred to the intensive care unit (ICU) was determined on patient's recovery from anesthesia and hemodynamics, and postoperative procedures were performed with self-administered intravenous analgesia.

Data collection

The primary outcome in this study was the incidence of postoperative hepatic insufficiency. Postoperative hepatic insufficiency was determined using total serum bilirubin >50 μmol/L and/or prothrombin activity <50% on postoperative day 5 as proposed by Balzan et al. [8]. Secondary outcomes included postoperative length of hospital stay, in-hospital mortality, ICU admission after surgery, rate of mechanical ventilation in the ICU, duration of mechanical ventilation, and length of stay in the ICU.

Baseline demographic data included age, sex, body mass index (BMI), ASA classification, hemoglobin concentration, prothrombin time, alanine aminotransferase, aspartate aminotransferase, albumin, total protein, hematocrit, Child liver function classification, blood urea nitrogen, serum creatinine concentration, glomerular filtration rate, and comprehensive complication index (CCI) (**Table 1**). Intraoperative data included operative time, anesthesia time, hepatectomy time, mean CVP during hepatectomy, MAP during hepatectomy, transfusion rate, cumulative hepatic vascular occlusion, in-

Table 1. Charlson comorbidity index and weighting of comorbidities

Comorbidity	Point (s)
Myocardial infarct	1
Congestive heart failure	1
Peripheral vascular disease	1
Dementia	1
Cerebrovascular disease	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes	1
Leukemia	2
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with end-organ damage	2
Any tumor	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
AIDS	6
Age	
<50 years	0
50-59 years	1
60-69 years	2
70-79 years	3

AIDS: Acquired Immune Deficiency Syndrome.

traoperative fluids, urine volume, and blood loss.

Statistical analysis

Propensity score matching was used to perform randomized strategy equilibria on the non-essential confounding factors of the retrospective study to reduce selection bias. The baseline data were included as an independent variable in logistic regression analysis to obtain the propensity value of each case. Cases with the same or similar propensity values were matched at 1:1.

Data analysis was performed using SPSS 22.0. Normally distributed measurement data were expressed as mean ± standard deviation ($\overline{x}$±sd), and comparisons between groups were made using the two independent samples t-test; non-normally distributed measurement data were expressed as median (interquartile range) [M (IQR)]. Comparisons of count data were made using the χ^2 test or Fisher's exact test. Significance was set at $P<0.05$.

Results

Between October 1, 2014 and October 30, 2020, a total of 331 patients with primary liver cancer underwent laparoscopic major hepatectomy. Among them, 6 had a preoperative diagnosis of hepatic insufficiency, 5 were converted from laparoscopic to open surgery intraoperatively, 2 experienced intraoperative cardiac arrest, and 4 had incomplete data; 89 patients from each of the two groups were included in the study after successful matching.

Comparison of baseline data

Baseline data before matching showed that compared with the NCVP group, the CLCVP group had a greater age distribution, higher BMI, a higher proportion of people with Child liver function class B, and a higher CCI, and after successful matching, there was no significant difference in baseline data between the two groups (**Table 2**).

Comparison of intraoperative data

After propensity score matching, intraoperative data differed significantly between the two groups, and patients in the CLCVP group had shorter anesthesia time, operative time, cumulative hepatic vascular occlusion, and surgery time, smaller CVP values, less bleeding, and less intraoperative blood transfusion than those in the NCVP group. Patients in the CLCVP group had less fluid rehydration before induction compared with the NCVP group due to fluid restriction. However, there was no significant difference in intraoperative fluids ultimately between the two groups (**Table 3**).

Comparison of postoperative outcomes

The incidence of postoperative hepatic insufficiency did not differ between patients in the CLCVP and NCVP groups, and the differences in other postoperative indicators, including postoperative length of hospital stay, in-hospital mortality, postoperative ICU admission, rate of mechanical ventilation in the ICU, duration of mechanical ventilation, and ICU residence time, were not significant ($P>0.05$) (**Figure 1**).

Table 2. Baseline variables used for propensity score matching

Variable	Before propensity score matching			After propensity score matching		
	CLCVP group (n=143)	NCVP group (n=101)	*P* value	CLCVP group (n=84)	NCVP group (n=84)	*P* value
Age (years)	59.73±6.71	54.21±7.40	0.011	54.39±8.07	54.82±7.23	0.284
Male gender (%)	77.62	78.22	-	70.31	69.84	-
Body mass index (kg/m^2)	23.46±3.67	21.79±3.84	0.026	20.89±3.50	21.03±3.72	0.094
ASA classification						
I/II (%)	72.03	71.29	-	70.83	71.04	-
III (%)	27.97	28.71		29.17	28.96	
Hemoglobin (g/L)	118.61±9.41	114.93±9.86	0.126	116.33±9.28	114.07±9.77	0.103
Prothrombin time (s)	10.24±1.95	10.37±1.87	0.311	10.08±1.79	10.19±1.92	0.367
Alanine aminotransferase (μ/L)	42.37±5.14	40.91±4.92	0.104	40.97±5.02	40.85±5.11	0.508
Aspartate aminotransferase (μ/L)	40.70±5.26	39.87±5.01	0.417	40.11±5.91	40.02±6.15	0.401
*Alb*umin (g/L)	39.81±6.03	41.35±5.94	0.096	40.64±6.83	40.82±7.01	0.073
Total bilirubin (μmol/L)	15.29±2.52	14.94±3.08	0.073	14.88±2.74	15.02±2.95	0.092
Hematocrit	0.38±0.06	0.39±0.05	0.132	0.37±0.07	0.38±0.06	0.224
Child-Pugh						
Class A (%)	68.32	79.21	<0.05	75.50	76.04	-
Class B (%)	31.68	20.79		24.50	23.96	
Blood Urea Nitrogen (mmol/L)	17.16±3.75	15.89±3.23	0.069	16.84±3.55	16.62±3.60	0.371
Serum creatinine concentration (μmol/L)	76.21±8.49	79.33±8.71	0.092	77.05±8.73	76.92±9.07	0.215
Glomerular filtration rate [mL/(min·1.73 m^2)]	96.02±9.31	95.37±9.84	0.273	95.23±9.94	94.81±9.75	0.085
Charlson complication index	3.71±0.37	3.10±0.41	0.034	3.17±0.28	3.20±0.31	0.117

Data are presented as percentage or mean ± sd; CLCVP: Controlled low central venous pressure; NCVP: Normal central venous pressure; ASA: American Society of Anesthesiologists.

Table 3. Intraoperative variables after propensity score matching

Variable	After propensity score matching		
	CLCVP group (n=84)	NCVP group (n=84)	*P* value
Operative time (min)	240.24±20.46	271.43±30.73	0.040
Time for hepatectomy (min)	64.39±8.97	78.31±10.68	0.009
Average CVP during hepatectomy (cmH_2O)	3.25±0.39	8.07±1.15	0.019
Average MAP during hepatectomy (mmHg)	84.33±9.95	85.07±9.29	0.178
Blood transfusion (%)	14.57	20.34	0.027
Cumulative hepatic vascular occlusion (min)	51.06±7.71	56.58±7.62	0.037
Anesthesia time (min)	268.42±24.71	295.54±38.61	0.013
Intraoperative fluids			
Infusion volume before anesthesia induction (ml)	400 (100-600)	650 (300-850)	0.021
Total fluid infusion (ml)	2500 (1500-3500)	2500 (1000-3000)	0.204
Urine volume (ml)	750 (300-900)	900 (400-950)	0.016
Blood Loss (ml)	600 (200-750)	600 (200-800)	0.043

Data are presented as mean ± sd or median (interquartile range); CLCVP: Controlled low central venous pressure; NCVP: Normal central venous pressure; MAP: Mean arterial pressure.

Discussion

The results of this propensity score-matched, retrospective study showed that for patients receiving laparoscopic major hepatectomy, the incidence of postoperative hepatic insufficiency in patients with CLCVP during lobectomy was 21.23%, which had no significant difference from the incidence of postoperative hepatic insufficiency in patients with NCVP (21.54%). This shortened the time for hepatectomy and operative time, reducing intraoperative bleed-

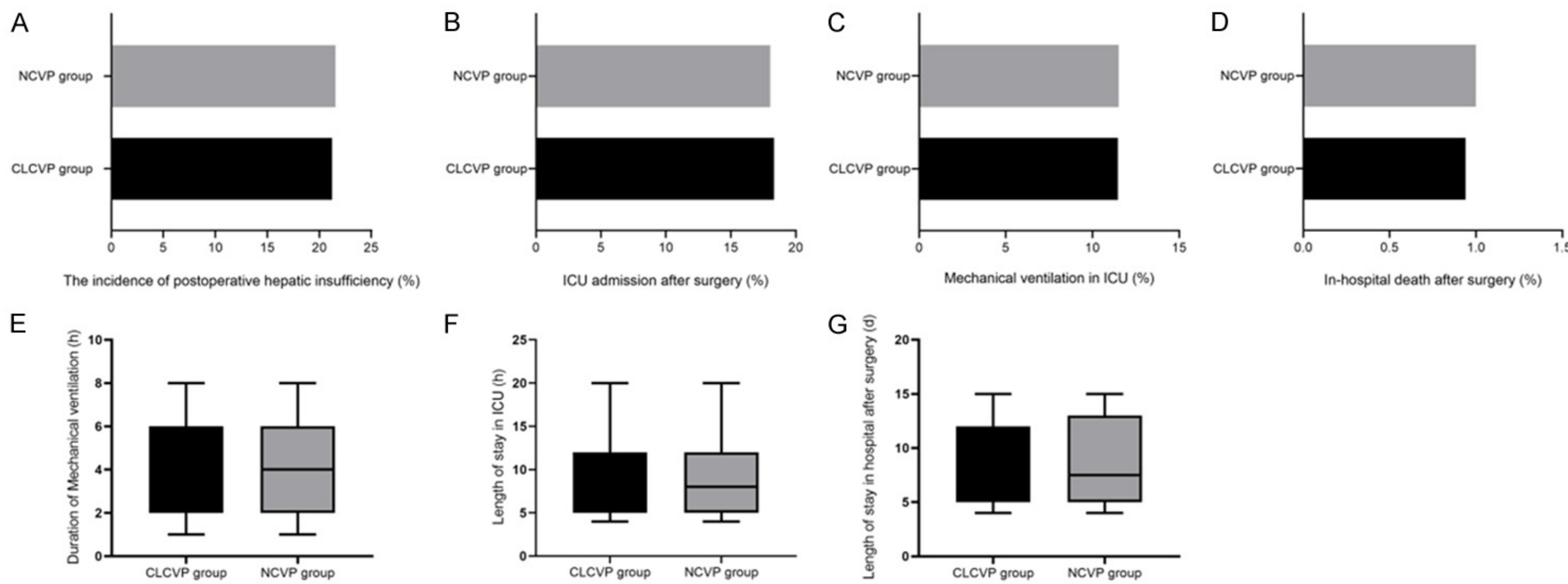

Figure 1. End points of the study used for propensity score matching. The postoperative outcomes showed no significant difference between the two groups (*P*>0.05). CLCVP: Controlled low central venous pressure; NCVP: Normal central venous pressure; ICU: Intensive care unit.

ing, without negative effects on patients' postoperative length of stay, ICU admission, or mortality during hospitalization. In conclusion, this study further confirmed the effectiveness and safety of the CLCVP procedure.

The resection of more than three liver segments is associated with higher postoperative mortality and complications than the resection of less than three liver segments, and therefore the resection of four or more liver segments is defined as major hepatectomy [9]. The most serious complication after major hepatectomy is liver failure, with an incidence of 1.2%-32% [10], which is manifested as progressive jaundice, coagulation disorders, cerebral dysfunction, and multi-organ failure, with a mortality rate of 1.6%-1.8% [11, 12]. Studies have shown that patients with hepatocellular carcinoma have significantly higher levels of aspartate aminotransferase and alanine aminotransferase on days 1, 3, and 7 after liver surgery, suggesting delayed recovery of postoperative liver function [13, 14]. Intraoperative bleeding of >1200 mL is an independent risk factor for postoperative liver failure [15], and intraoperative hepatic blood flow is often blocked before hepatectomy to minimize bleeding. However, blocking and opening of the hepatic portal can lead to hepatic ischemia-reperfusion injury [16], and both severe hypotension and prolonged blocking of hepatic blood flow can lead to significant hepatic hypoxia-ischemia [15], which will eventually affect the recovery of liver function. Therefore, the duration of hepatic portal block should be limited during hepatectomy, and total hepatic vascular occlusion should be performed as little as possible. More hemihepatic vascular occlusion or highly selected hepatic vascular occlusion should be performed to reduce ischemic injury to the residual liver. Liver resection with CLCVP can also reduce bleeding with high head and low foot positions, and complete muscle relaxation. In addition, the incidence of postoperative liver failure can be reduced by optimizing the patient's preoperative nutritional status and reducing intraoperative blood loss and transfusion rate [4, 17, 18]. Therefore, anesthesiologists should pay more attention to the protection of liver function and reduce the damage caused by organ hypoperfusion and hypoxia to the liver. The present retrospective study explored the effect of CLCVP during anesthesia on postoperative hepatic insufficiency.

After intraoperative occlusion of the first hepatic portal vein, hemorrhage mostly originates from the hepatic vein and hepatic sinusoids. With the decrease in the pressure of the inferior vena cava, the pressure of the hepatic vein and hepatic sinusoids also decreases. Studies have shown that the pressure of the inferior vena cava and the pressure of the right atrium are significantly consistent. Decrease of CVP can reduce the pressure of the hepatic vein and hepatic sinusoids [19]. Therefore, controlling CVP at a lower level during lobectomy is conducive to blood return to the hepatic venous system, thereby reducing intraoperative bleeding and reducing difficulty in surgical operations [20]. Similar results were obtained in this study, *i.e.*, intraoperative bleeding was decreased in the CLCVP group, providing the operator with a clearer operative view, shorter operative time, and shorter cumulative hepatic vascular occlusion in the hepatic portal, thus reducing the overall operative time and anesthesia time.

In terms of the safety of CLCVP technique, the abdominal pressure is usually set at 14 cmH_2O during laparoscopic major hepatectomy. When the fissure of the hepatic vein is large, the gas in the abdominal cavity tends to enter the body circulation through the hepatic vein, leading to gas embolism [21]. It has been found that the incidence of gas embolism during liver surgery is significantly higher when manually established pneumoperitoneal pressure/CVP is increased, and it is recommended that when surgery is performed around the larger hepatic veins, the pneumoperitoneal pressure should be appropriately reduced and the CVP should be increased to reduce the pneumoperitoneal pressure/CVP ratio and avoid severe gas embolism [22]. On the other hand, although it has been demonstrated that the CLCVP technique can reduce bleeding, shorten operative time, hepatic portal occlusion time and length of hospital stay, facilitate patient recovery, and improve postoperative survival, it also poses a risk of hypoperfusion to vital organs [6, 23-27].

The main measures for CLCVP include restricting fluid intake and dilation of arterial blood vessels with vasoactive drugs, which reduces the effective circulating blood volume and volume returning to the heart. This leads to a decrease in cardiac output and bringing varying degrees ofhypoperfusion to organs, and if this status persists for a long time, tissue and organ damage may occur and affect postoperative recovery. In the present study, it was found that although CVP was controlled at a low level during hepatectomy by measures such as limiting fluid intake, measures were also taken to avoid a decrease of MAP and to ensure perfusion of vital organs. The results of the present study demonstrated the advantages of CLCVP for surgical operations, but there was no difference between the NCVP and CLCVP groups in terms of postoperative length of hospital stay, postoperative in-hospital mortality, ICU admission, or duration of mechanical ventilation. This may be related to the fact that we maintained intraoperative MAP and ensured vital organ perfusion, which seemed to be of great importance for the patient's postoperative recovery.

In terms of optimal control values for CVP, it has been shown that CVP <1 mmHg during lobectomy, along with phenylephrine infusion to maintain arterial pressure, can increase the body's lactate levels, suggesting that organ hypoperfusion may be associated with CVP <1 mmHg [7]. Controlling CVP at 2.1-3 mmHg can reduce bleeding and prevent damage to important organs. This level has no significant effect on the body's oxygen supply, oxygen consumption, or oxygen metabolism rate [28]. Oxygen supply, oxygen consumption, and oxygen metabolic rate were significantly reduced when CVP was below 2 cmH_2O [29]. Similarly, in this study, the CVP of patients in the CLCVP group was not continuously reduced, but was controlled to 2-3 cmH_2O.

There are several limitations of this study. First, although the propensity score matching method was used to reduce selection bias, we still could not completely exclude the possibility of unobserved differences between the two groups. Second, intraoperative hemodynamic stability could not be determined, which may affect patient prognosis. Finally, patients were not followed up after discharge, and the effect of CLCVP on the long-term prognosis of patients needs to be further confirmed.

In conclusion, intraoperative CLCVP did not increase the incidence of postoperative hepatic insufficiency compared with NCVP in patients undergoing laparoscopic major hepatectomy, nor did it significantly affect postoperative outcomes such as postoperative length of hospital stay and in-hospital mortality, further confirming the safety of the CLCVP technique.

Disclosure of conflict of interest

None.

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